UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF INDIANA
INDIANAPOLIS DIVISION

ELI LILLY AND COMPANY, Plaintiff, vs. TEVA PARENTERAL MEDICINES, INC., APP PHARMACEUTICALS, LLC, PLIVA HRVATSKA D.O.O., TEVA PHARMACEUTICALS USA, INC., BARR LABORATORIES, INC., Defendants.	) Cause No.) 1:10-CV-01376-TWP-DKL) Indianapolis, Indiana) **August 19, 2013**) 9:03 a.m.

V O L U M E I

Before the Honorable
TANYA WALTON PRATT

OFFICIAL REPORTER'S TRANSCRIPT OF
BENCH TRIAL

Court Reporter: David W. Moxley, RMR, CRR, CMRS
United States District Court
46 East Ohio Street, Room 340
Indianapolis, Indiana 46204

PROCEEDINGS TAKEN BY MACHINE SHORTHAND
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I N D E X

I N D E X O F E X H I B I T S

(In open court.)

THE COURT: Good morning, everyone.

We are on the record. This is Eli Lilly and Company, plaintiff, versus Teva Parenteral Medicines, APP Pharmaceuticals, Pliva -- how do you pronounce the --

MR. WIESEN: Your Honor, unfortunately, I still haven't been able to determine how to pronounce that Croatian term.

THE COURT: But it is spelled H-R-V-A-T-S-K-A Pharmaceuticals, U.S.A -- I'm sorry -- Teva, Teva Pharmaceuticals U.S.A. and Barr Laboratories are the defendants, and our case number is 1:10-CV-1376. And we are here this morning for a bench trial on a patent infringement matter.

And why don't we have attorneys state their names for the record, beginning with the plaintiff's table?

MR. PERLMAN: Good morning, Your Honor. Adam Perlman from Williams & Connolly on behalf of the plaintiff, Eli Lilly. If I can introduce the remainder of our table, to my left, my colleague Bruce Genderson.

MR. GENDERSON: Good morning.

MR. PERLMAN: Mr. Dov Grossman.

MR. GROSSMAN: Good morning, Your Honor.

THE COURT: Good morning.

MR. PERLMAN: David Krinsky.

MR. KRINSKY: Good morning, Your Honor.

THE COURT: Good morning.

MR. PERLMAN: Behind Mr. Krinsky, Megan Hughes.

MS. HUGHES: Good morning, Your Honor.

THE COURT: Good morning.

MR. PERLMAN: Andrew Trask.

THE COURT: Good morning.

MR. PERLMAN: Back at the table, in-house from Eli Lilly, Steve Caltrider.

James Leads, also from Eli Lilly.

THE COURT: Good morning.

MR. PERLMAN: Of course, you know Jan Carroll from Barnes & Thornburg.

MS. CARROLL: Good morning.

THE COURT: Good morning, Counsel.

MR. PERLMAN: I have a couple more introductions, Your Honor. In the courtroom we have Sue Mahoney, who is the president of Lilly Oncology.

THE COURT: Good morning.

MR. PERLMAN: And we also have Michael Harrington, who is the general counsel of Eli Lilly & Company.

THE COURT: Good morning.

All right. Thank you, Mr. Perlman.

And at our defendant's table?

MR. WIESEN: Good morning, Your Honor.

Daryl Wiesen from Goodwin Procter on behalf of all the defendants, and with me today I have Emily Rapalino from Goodwin Procter.

THE COURT: Good morning.

MR. WIESEN: Michael Cottler from Goodwin Procter.

MR. COTTLER: Good morning, Your Honor.

THE COURT: Good morning.

MR. WIESEN: Elaine Blais.

MS. BLAIS: Good morning, Your Honor.

MR. WIESEN: Kandi Hidde from Bingham Greenbaum.

THE COURT: Good morning.

MR. WIESEN: And out in the gallery we have Brian Prew and Natasha Daughtrey from Goodwin Procter.

THE COURT: Good morning.

MR. WIESEN: And from the clients, Jon Wise from Teva Pharmaceuticals and Jack Silhavy and Ali Ahmed from Fresenius Kabi, formerly APP Pharmaceuticals.

THE COURT: Okay. Good morning.

And before we begin, I do apologize that it's so very warm in here, but apparently it's a building-wide problem, and they're working on it, and it should get cooler as the day progresses. So we'll just have to grin and bear it.

All right. Lawyers, I think we're going to begin with the tutorial, and how are you all going to do that

presentation? The Court gave you 30 minutes total.

MR. PERLMAN: So, Your Honor, when I proposed doing this, I said it would be objective and nonadversarial, and Mr. Wiesen and I have worked out a joint presentation.

THE COURT: Wonderful.

MR. PERLMAN: And so the way we thought we would do it is that we would both stand here. We've divided it up, so we're each taking certain parts. The other one may chime in, if necessary. We're optimistic it's not going to happen much --

THE COURT: Okay.

MR. PERLMAN: -- but we're going to give it a whirl.

THE COURT: Sounds good.

MR. WIESEN: And we've jointly prepared a set of slides, as well, that took a little negotiating but we think might be helpful.

MR. PERLMAN: It might be helpful if I hand those up.

THE COURT: You may.

Thank you. If you have one for the clerk -- Tanesa, you don't need one, or do you?

MR. PERLMAN: The law clerk.

THE COURT: The law clerk.

Do you want one, Tanesa?

David, the court reporter might.

All right. Counsel, you may.

MR. PERLMAN: Thank you, Your Honor.

As you know, this case is about pemetrexed, which is an antifolate, and so we'll begin with a discussion of what a folate is and the folate pathway.

"Folates" is a term that refers to a class of compounds that are essential for various biochemical reactions in the human body. Those processes include synthesizing several of the major building blocks of DNA and RNA. Folates occur naturally in a variety of foods, and there are a variety of different forms of folate that the body uses. And they are generally referred to as reduced folates, which is a term that you're going to hear a bunch in this trial.

The body makes various forms of reduced folates from the folates that people obtain from food. Another example of a folate is folic acid, which you may have heard of. It's a vitamin. Folic acid is the most common folate used as a dietary supplement, but it doesn't occur widely naturally in nature. For a variety of reasons, that's the form that's most easy to put into a pill, and so that's what you can buy at the health food store.

Folic acid is not itself usable by the body, but the body converts it into reduced folates that the cells of the body can use. Now, within the cells in the human body, there are what are called enzymes, which are substances that carry

out various reactions that, among other things, help transform one molecule into another molecule. As relevant to this case, there are a number of different enzymes in cells in the human body that convert one folate into another form of folate and which as part of the same reactions also cause chemical changes to other compounds that you're going to hear about.

Now, the various reactions that convert one form of folate to another form of folate within the body are referred to as the folate pathway, or the folate cycle sometimes, and that's what we have up on the screen. Now, nobody panic. We don't have to understand the entirety of this diagram in order to follow this case. But what I wanted to show you is the whole thing is complicated, and what you're seeing here is a cycle where various enzymes facilitate a series of reactions in which different forms of folate are used to make a host of different products. And what happens is the various forms of folates cycle through this process over and over again.

Now, I'm going to highlight three of these that are going to play a role in this case. They are TS, DHFR and GARFT. And they each have an impenetrably long technical name, but they are commonly referred to by these acronyms, and we're going to endeavor to do that here so as to avoid confusion.

THE COURT: Okay.

MR. PERLMAN: Let's focus in on the part of the

pathway that uses these enzymes, and there's also a fourth one on here that we circled called AICARFT. Each of these enzymes is involved in chemical reactions that use folates in order to make various building blocks of DNA. So, the folate interacts with the enzyme, a particular reaction occurs, and the output of it is something that is usable by the cell to make DNA.

Cells need DNA in order to be able to divide and grow and produce more cells, and cells need to do that or they can't stay living. And so the process by which these enzymes convert folate into DNA is necessary for cell division and reproduction.

Now let's talk about antifolates. Pemetrexed, which is the compound Lilly sells as Alimta, is an antifolate. Antifolates are a class of compounds that interfere with the natural reactions of the folates. So, the idea is to block the cell division and thus kill cancer cells by doing so because the cancer cells are dividing out of control, and if you prevent them from making DNA, they can't divide anymore, and the idea is you'll kill the cancer.

So, the folates work, as I said, by binding to the various enzymes that I put on up on the screen. Antifolates work by binding to the same enzyme in place of the folate. When the antifolate binds to the enzyme, the antifolate doesn't allow the enzyme to run the reaction that it would normally want to do with the folate; and the building block of

DNA that it would normally make can't get made. It's not a perfect analogy, but the way this is commonly thought of is, think of the enzyme like a lock, and the folate and the antifolate are both keys that fit into the lock, but only the folate can turn the lock. And so when the antifolate is in the lock, it blocks the folate from getting there, and also the lock doesn't turn, and so the reaction that the lock begins doesn't take place.

And so the concept behind using antifolates to treat cancer is that the antifolate will compete with the natural folate for interaction with these enzymes in the folate pathway and disrupt the ability to make DNA. So, I'm showing this here graphically. Antifolates, it's not sort of one size fits all. The different antifolates inhibit the enzymes of the pathway to a different degree and different strength, depending on which particular antifolate you're talking about.

The example that I've put on up on the screen, one of the enzymes pemetrexed blocks or inhibits is the enzyme TS, and so the X is indicating that pemetrexed would interact with TS and block the folate from interacting with TS.

The effect of that is blocking the synthesis of one of the building blocks of DNA. This is the rationale, or one of the rationales, by which pemetrexed treats cancer. The idea is that the antifolate binds to and interacts with the enzyme instead of the reduced folate, and then the rest of

this process sort of to the left of where the upper X is doesn't happen, and the DNA doesn't get made.

And so let's do it graphically. On the previous slide, the DNA was made, the cells split, you had more cells, and in the case of cancer, the cancer would continue to grow. The rationale behind using an antifolate for chemotherapy is that cancer cells divide more often than many normal, healthy cells. And because that cell division requires DNA, rapidly dividing cells like cancer cells need more DNA than less rapidly dividing cells. And so when you interfere with the action of one or more of the enzymes involved in making the building blocks of DNA, you can -- that can lead to inhibition of tumor growth, death of the tumor cells and shrinkage or elimination of the tumor.

The problem is, that happens in all cells, not just cancer cells, the blocking of the making of DNA. And there are also healthy, normal cells in the body that divide rapidly like cancer cells do. Examples might be in the bone marrow or the gastrointestinal tract. Antifolates affect them, too, which leads to certain toxicities or severe side effects for the patient that you'll hear about during the trial.

MR. WIESEN: Another thing we're going to be talking about during the trial, Your Honor, is the concept or something called the homocysteine. Homocysteine is another substance that's in the body, mainly in the blood, and you can

measure how much homocysteine there is in the blood of an individual person. There are a number of reasons that homocysteine might be elevated, might be high, in a person's blood, and some of those reasons are related to the folate pathway that we've been talking about.

We've put up on the slide that we've circled where in the folate pathway you can see homocysteine plays a role, just to orient you on the complicated graphic that Mr. Perlman showed you earlier. And similarly, we can show you a smaller part of the pathway that includes the homocysteine reaction that you'll hear about. And let me walk you through what's going on here.

We created a graphic that's, I think, a little bit more accessible than the pathway as drawn by some of the experts so we can show what's going on.

At one point in the pathway there's a reaction between two substances called -- homocysteine is one of them. We have that on the left here in orange; and on the right, we have what's called MTHF. That's one of the reduced -- one of the specific reduced folates that Mr. Perlman was referring to, and even though MTHF is a reduced folate, importantly, it cannot be used by any of the enzymes in the folate pathway to make DNA. We put that on the slide. This one can't be used to make DNA, and there's only one way in which this MTHF or methyltetrahydrofolate, some of the experts will refer to it

as, can be converted to a form of folate that then becomes usable elsewhere in the pathway. And it's through this reaction that we're about to run through.

So when the cell operates properly, there's a chemical reaction between homocysteine and methyltetrahydrofolate or MTHF. And it takes part in an enzyme that we've shown just as a chemical reaction in the middle. And the output of that is called THF or tetrahydrofolate and the substance called methionine.

The homocysteine gets converted. The methionine, the MTHF gets converted to THF, and the -- unlike the MTHF, the THF is an active folate that the other enzymes in the cell can use. So it's important that the MTHF be converted by this process into THF. If for whatever reason this reaction doesn't happen and the MTHF is not converted to THF or that doesn't happen efficiently -- it may happen some but not enough in the cell -- the folate, which is now stuck in the MTHF form is often referred to as trapped because it's stuck in a form that the cells can't use to make DNA.

And this concept you will hear described as the methyl trap or the methyl folate trap, and what that's referring to is that the reduced folates are trapped in the MTHF form that can't otherwise be used in the pathway. So let us show you what happens if the patient is folate deficient, and we're going to start with an extreme example.

Let's assume somebody has absolutely no folate or no MTHF. That's not really going to happen but for explaining the process, the concept is useful. If that's the case, then this process won't proceed. If there's no MTHF to go into the chemical reaction, the chemical reaction doesn't occur and the homocysteine can't be converted into methionine.

If the homocysteine is not converted into methionine, the amount of homocysteine in the blood goes up. And so you can -- and in the absence of the folate and the absence of the THF, which is also not created when there's no MTHF, that will have an impact on the other parts of the folate pathway where these folates come out and continue to cycle through. For the purposes of the tutorial, we're still just going to stay focused on this reaction, but it's important that you understand this is a small part of the bigger reaction that occurs.

The same thing basically happens if a patient is low in folate, not none but low, what will happen is that the reaction will happen some. It will form some -- the MTHF will go through the chemical reaction with homocysteine and THF, with a little bit of THF and methionine will be formed, but the amount of homocysteine in the blood will still go up because there's not enough MTHF to have the reaction run as efficiently as possible.

So if there's a folate deficiency, the amount of

homocysteine in the patient's blood will go up. It keeps being formed by the cycle but isn't transformed from homocysteine to methionine. And that's why elevated homocysteine is referred to sometimes as a marker or a signal that a patient may be folate deficient.

You are also going to hear some about vitamin B12 in this case. Vitamin B12 also plays into this reaction. Although it's unrelated to folate, like folate, vitamin B12 is an essential nutrient. It's a vitamin, and up until now we've been calling this chemical reaction literally a black box on the slide. Well, let's take a look at a little bit more what happens in the reaction. There we go.

The enzyme that's involved in the transformation of MTHF to THF has the roll-off-your-tongue name methionine synthase, and there's not a great abbreviation for that one. It's what people tend to call it, unfortunately. Vitamin B12, as we've shown here, fits into -- or actually it's technically a derivative of vitamin B12, is necessary for this reaction to proceed. It's called the cofactor, and it helps the methionine synthase process this reaction.

So let's assume for a minute there's no B12, back to our extreme example, this time with no B12. We've got plenty of MTHF but no B12. The process doesn't go forward, the reaction doesn't occur, and homocysteine builds up in the cell in the same way and in the blood the same way as if there were

no folate.

Let's look at the same situation if there's a deficiency, a small amount of B12 but not a full amount to have the reaction run efficiently. Again, some homocysteine is converted to methionine. Some methyltetrahydrofolate or MTHF is converted to THF, but the homocysteine will go up in the blood because the conversion is not happening efficiently. And this is why elevated homocysteine can also be an indicator of a vitamin B12 deficiency. Because with both folate deficiency or vitamin B12 deficiency, you can see the homocysteine go up because this particular reaction doesn't run efficiently.

Now, there's at least one more substance in the blood that's going to come up in the trial. It is called methylmalonic acid. It's actually a term that's in the patent as well. That one does have an abbreviation, it tends to be called MMA, and we'll try and call it that.

MMA is not involved in the folate pathway. If a patient has elevated amounts of MMA in their blood, that, however, can be a marker for a deficiency of B12 as well because of yet another reaction that we'll show you. There's another reaction in the totally different part of the cell, and for our purposes in this case, what that reaction is, what it's used for really doesn't matter at all. And we're not even really going to talk about it.

What's important for us to understand is that there's this substance called methylmalonyl-CoA. We're showing that on the slide, and the methylmalonyl-CoA interacts with another enzyme. And the way, if you catch on, the way these are often named is there's an "ase" added at the end, so methylmalonyl-CoA mutase is the enzyme that converts methylmalonyl-CoA.

And what happens with vitamin B12 is it acts here as well to assist in a particular conversion of methylmalonyl-CoA to succinyl-CoA, and for this reaction to occur, vitamin B12 is required. If the patient doesn't have enough vitamin B12, like we were looking at in the other reaction, the methylmalonyl-CoA gets converted to something else called MMA, and so that -- in this situation, in this other reaction, a shortfall of vitamin B12 can lead to an increase in the presence of MMA in the blood, and so MMA can also be a marker or a signal that there's a deficiency of vitamin B12.

MR. PERLMAN: All right. So just to sort of recap where we are, elevated homocysteine can be the result of low levels of folate or low levels of B12, as well as other things. Elevated MMA is an indicator of low levels of B12, and so if you look at both substances at the same time, that can help distinguish what type of deficiency a patient has. So we've put together a graphic that hopefully will be helpful in explaining this.

We're purposely oversimplifying here to focus just on folate and vitamin B12 as potential causes for elevated homocysteine. There are other causes, but for the tutorial, this is complicated enough. All right. So in the first slide, as a patient's folate levels go down, the homocysteine levels will go up, which is why elevated homocysteine can be an indicator of low folate.

Now, let's add B12 to the equation. When B12 levels go down, homocysteine goes up and MMA goes up. And so the combination of these two markers allows doctors to try to narrow down the reasons for why a patient might have elevated homocysteine. If the homocysteine is elevated but the MMA is not, that indicates that whatever is causing the homocysteine to go up, it is probably not a vitamin B12 deficiency, because if there were a vitamin B12 deficiency, the MMA levels would probably go up too.

Now, on the other hand, if both homocysteine and MMA levels are elevated, that indicates that the patient likely has at least low levels of vitamin B12. Now, there may also be other causes for the elevated homocysteine, like low levels of folate, but what you can at least conclude in that situation when both markers are up is that low levels of B12 are likely playing a role in the elevated homocysteine.

MR. WIESEN: Your Honor, the case is also going to go beyond just this folate pathway.

MR. PERLMAN: Very disappointing.

MR. WIESEN: I know. Something else you will hear about in the case is the drug development process. After a new drug is discovered, work is done to develop the drug and determine whether it can be safely and effectively given to patients. Work begins in the preclinical phase. This refers to before it's given to humans. And it includes tests in test tubes, in cells, in live animals, but not humans.

From the preclinical phase, if a drug looks successful and promising, a drug may move into clinical trials, and those clinical trials are generally considered in different phases, which you will hear about in the case. The first clinical trials, the first trials in humans -- clinically usually are first in humans -- are called Phase 1 trials, and these are designed principally to figure out a safe dose for patients. They can provide other information as well, and there will be an issue in the case about how and what other information can be ascertained from such trials.

One thing we should note is that Phase 1 clinical trials for chemotherapy drugs, in general, are a little different than most Phase 1 trials. For most Phase 1 drugs, the trial is conducted in healthy patients. But for chemotherapy drugs, they're conducted in patients who have cancer because the drugs can have serious toxicities associated with them for all the reasons we've just talked

about, about what chemotherapy drugs and antifolates can do.

Phase 2 trials, not surprisingly, come after Phase 1 trials. They're usually done using the safe and promising doses and schedules that were determined in a Phase 1 trial. Phase 2 trials usually focus on trying to determine if the drug works in a particular type of cancer rather than in cancer generally.

And following Phase 2 trials, if there are promising results, a drug may move into a phase three phase or phase three trials. Phase three trials are controlled trials for FDA approval of the drug, and they measure both safety and efficacy and are almost always required by the FDA before they will approve a drug.

MR. PERLMAN: And so that concludes our prepared tutorial. We brought it in about six and a half minutes early, and so if Your Honor has questions, we're happy to answer those or else we're happy to proceed.

THE COURT: That was helpful, very helpful. We can move into opening statements and --

MR. WIESEN: We've agreed the defendants will go first since we have the burden of proof. I have binders with slides if people would like them. We'll also show them on the screen. I can distribute them.

THE COURT: I would like one.

MR. WIESEN: Good morning, Your Honor.

THE COURT: Good morning, Counsel.

MR. WIESEN: The defendants in this case are two pharmaceutical companies, Teva Pharmaceuticals and Fresenius Kabi, which was previously known as APP Pharmaceuticals. What brings us here today is that each of these companies has told the FDA that they believe the patent-in-suit is invalid, and have requested that the FDA approve their applications to manufacture and sell a generic versions of Eli Lilly's pemetrexed product.

The regulatory filing that both of the companies made challenges the '209 patent, and is part of a legal structure that Congress put in place nearly 30 years ago to allow companies like the defendants to challenge patents and attempt to bring less expensive generic products to market.

In 1984, Congress passed the Hatch-Waxman Act. The statute allows the generic pharmaceutical company to file what's called an Abbreviated New Drug Application, which is usually called an ANDA, A-N-D-A. The application is called abbreviated because the generic companies can rely upon the safety and efficacy data developed by the brand company. This allows the generic companies to develop their products for less money, allows them to sell the products to patients and doctors at substantial discounts.

In adopting the Hatch-Waxman Act, Congress sought to establish a balance between branded and generic pharmaceutical

companies. As part of that balance, Congress adopted 35 U.S.C. 271 E. It's that section of the U.S. code of the patent statute that allows Eli Lilly to bring this lawsuit before the generic companies have launched a product.

In adopting the act, Congress recognized branded companies would have an incentive to seek as many patents as possible to extend their monopoly as long as possible. The act is designed to allow generic companies, as both Teva and Fresenius to challenge those patents in court and ensure that a monopoly is not improperly extended by an invalid patent.

There's no dispute in this case that under this structure, Lilly's been able to reap substantial benefits from its development of pemetrexed. No matter what the results of this case, Lilly will have at least 13 years of exclusive sales, allowing them to make billions of dollars in profits.

Lilly received an earlier primary patent on the pemetrexed molecule itself, which doesn't expire until 2017. And the reason that patent doesn't expire until 2017 is an extension they got as part of the Hatch-Waxman Act, part of the balance and tradeoff that Congress adopted.

Through this case, Lilly seeks to extend its exclusivity for another five years until 2022 by using a secondary patent, the '209 patent. The single patent at issue here doesn't claim pemetrexed as a molecule. It doesn't claim using pemetrexed to treat some new disease. They didn't

go find out "We thought it treated one thing, but it actually treats something else."

Instead, the patent claims only giving a combination of vitamins with pemetrexed on the idea that nutritional deficiencies in patients receiving chemotherapy may increase the toxicity or side effects for those patients.

The trial is going to focus on the invalidity of this patent over the next two weeks. The Court will hear testimony and evidence concerning invalidity defenses that can be put into two alternative categories. First, the assorted claims are obvious based on what would have been known by a person skilled in the art as of the filing date of the application, or actually a year before the filing date.

A person of ordinary skill looked at everything that was out there about antifolates, about the folate pathway, about pemetrexed. And including yet another Eli Lilly patent, they concluded that the claims are obvious and the patents should be declared invalid.

The second bucket of arguments that I'll get to in a little while concerns the disclosures in the patent specification. Simply put, although the patent purports to claim a regimen for effectively administering pemetrexed, it leaves out a critical detail. You can read the entire patent, and the thing you won't find is the dose and schedule to give pemetrexed. And that's a violation of another portion of the

patent statute.

Before we turn to the defenses in a little more detail, I want to spend a few minutes looking at the patent itself. It's TX1, and it's patent 7,727,209, which we'll call the '209 patent.

Initially in this case, Eli Lilly asserted all of the claims in the patent, and there are about 21 or 22 of them. But shortly before we filed the pretrial briefs, they dropped most of the claims, and we're litigating now only eight of them, Claims 9, 10, 12, 14, 15, 18, 19, and 21.

I've put up on the screen Claim 1, and some of the claims that are asserted are dependent claims. So they start with Claim 1 and add other details. And I want to spend a minute looking at it. Claim 1 is a method for administering pemetrexed disodium to a patient in need thereof comprising administering an effective amount of folic acid and an effective amount of methylmalonic acid lowering agent, followed by administering an effective amount of pemetrexed disodium wherein the methylmalonic acid lowering agent comes from this specified list.

In the trial, the case is going to focus on one methylmalonic acid lowering agent so we don't need to worry about most of the list. It's going to focus on vitamin B12. In many ways, although it may not look it, this claim is straightforward.

Claim 1 of the '209 patent claims giving these well-known vitamins, folic acid and vitamin B12, before giving a patient pemetrexed. It's all it covers. Previously, the Court has looked at this patent and entered a claim construction order that provides a little more clarity on what's covered by the patent. And I want to just note quickly two of the claim constructions entered by the Court.

First, the Court construed vitamin B12 to be cyanocobalamin, one of the specific B12 vitamins that falls into that general category, and much of the evidence in the case will therefore focus on cyanocobalamin.

Another claim term that was construed, I think through an agreement of the parties in the end, was the term effective amount of pemetrexed disodium. And for this case, that means an amount of pemetrexed disodium that is capable of providing a therapeutic benefit to the patient in need thereof.

So, if we look at this construction and think about the claims, all that is required by the claim is that the dosing regimen for pemetrexed be capable of providing a benefit to patients. And to prove that the claim is obvious, defendants need only prove it would be obvious what's claimed, that the invention would be capable of providing a benefit to patients.

We don't have to establish that it's obvious that

the FDA would have approved the drug. We don't have to establish that had Lilly sought a different dosing schedule, it would have failed. We don't have to establish that this is the best -- it was obvious that this was the best dosing schedule out there, because the claims don't require that.

All we have to prove is that the claims, as written and as construed, are obvious, and that's that it would have been obvious that giving folic acid and vitamin B12 pretreatment with pemetrexed would have provided a therapeutic benefit to a patient.

Now, the claims asserted by Eli Lilly in this case still do add some standard doses and schedules or administration routes for folic acid and vitamin B12 to the general concept of pretreating with vitamins. If we look at Claim 12, it serves as an example.

If we look at this, we see that what's added to the claim of giving pemetrexed is A, a particular dose of folic acid. That's 350 micrograms to about a thousand micrograms of folic acid, which is .35 milligrams to one milligram, if I'm doing my math right, and an administration of about 500 micrograms to about 1500 micrograms of vitamin B12. So, half a milligram to 1.5 milligrams.

The evidence in the case will be that these are standard doses of folic acid and vitamin B12 routinely administered by people of ordinary skill in the art.

Let me turn, then, to the first category of defenses. These two related but separate defenses, obviousness and obviousness-type double patenting, are based on what was known by a person of ordinary skill in the art before Lilly filed the patent application. The evidence will show that the claims of the patent were obvious based on a series of publications concerning antifolates generally and pemetrexed in particular. And when the Court considers all the evidence as a whole, as required by the patent statute, this evidence will establish that the claims are clearly and convincingly invalid.

Now, I want to note that many of the extensive publications and patents you're going to hear about concerning pemetrexed, before Lilly applied for the patent application here, were actually published by Lilly's own researchers.

Lilly didn't keep its research on this compound secret. They made a conscious choice to disclose and publish information on pemetrexed for all to see. Why they did that doesn't matter here. Whether it was done to keep their investors happy about how their pipeline was doing, or whether they were publishing it because scientific knowledge is useful and good to publish, it doesn't make a difference to this case.

What matters is that Lilly chose to disclose this research, and the law on the subject is clear. Once the

information is disclosed, it's given to the public. Lilly can't take it back later.

So for purposes of analyzing the validity of the patent, a person of ordinary skill in the art would have access to all of these publications. And we'll get to it in more detail in a minute, but not only did Lilly publish this information in abstracts and papers about pemetrexed, they also patented a method of administering an antifolate generally, which includes pemetrexed with folic acid pretreatment. That now expired patent, which I'll show you later is called the '974 patent, after the last three numbers in its patent, and it was filed years before the '209 patent.

The '974 is here. It's Trial Exhibit 916.

Let me turn to obviousness in a little more detail. As set forth by the Supreme Court nearly 50 years ago in Graham versus John Deere, obviousness requires the Court to consider evidence on four issues: The scope and content of the prior art, differences between the claimed subject matter and the prior art, the level of ordinary skill in the art, and secondary indicia of non-obviousness. We'll run through the evidence that you'll hear on each of these four factors.

Obviousness doesn't require that every element of the claim have been previously disclosed in one single prior art reference. To the contrary, obviousness generally assumes

that there isn't one reference that discloses all of the details of the invention.

The obviousness inquiry for the Court will be the question of whether, in light of all of the evidence, all of the prior art taken together, it would have been obvious to a person of ordinary skill in the art to combine that art and come up with the invention.

So what will the evidence be? Let's start with the scope and content of the prior art. The parties have worked together and stipulated to most of the prior art. We agree what is -- we could at least agree on publication dates for things, but that's not to say that there's nothing for this Court to decide.

The dispute's going to be about what the person of ordinary skill in the art would read from these references. When they sat down and read them, what would it teach? What would they take away from them?

Just a few minutes ago, we presented our joint tutorial on the technology in the case, and some of this will be undisputed. For example, pemetrexed is a chemotherapy drug in the class of antifolates. Dr. Mark Ratain, a well respected oncologist at the University of Chicago, with over 25 years of experience researching and treating cancer, will testify on behalf of the defendants. They will explain that like all chemotherapy drugs, pemetrexed -- excuse me, Your

Honor. They'll explain that like all chemotherapy drugs, pemetrexed kills cells in the body, killing as few healthy cells as possible while killing as many cancer cells as possible. But it's very difficult to achieve that balance.

The same way pemetrexed kills cancer cells by interfering with the folate pathway, as Mr. Perlman and I explained, is the same way it kills healthy cells. Killing the cancer cells is, generally speaking, good. It's why pemetrexed works as a chemotherapy agent.

The killing of healthy cells is bad. It explains most of the toxicity of pemetrexed. The evidence at trial will be that a person of ordinary skill in the art was looking for a dosing regimen for pemetrexed which, by 1999, was known as a very promising antifolate that hit the cancer cells as hard as possible while sparing as many of the healthy cells.

The folate pathway that the parties described earlier exists in cells throughout the body, and creates the building blocks for DNA which are necessary for cells to reproduce. The Court's going to hear a fair amount of testimony about this pathway beginning with Dr. Ralph Green, who's a distinguished professor at the University of California-Davis.

Dr. Green has spent his career studying folate and Vitamin B12 metabolism, and he'll explain the metabolic pathway and what a person of ordinary skill would understand

from that pathway in the context of the other available prior art about pemetrexed. Now, when a healthy person, eating a healthy diet, levels of folate and vitamin B12 are generally kept at certain levels that allow cells to efficiently reproduce through the process we described.

Some people also take over-the-counter multivitamins to supplement their diet. Either the natural folates or B12 from food or from a supplement play a role in the folate pathway or cycle. And without these vitamins, the cells can't reproduce. Antifolates have been in use since the 1940s to treat cancer. Doctors and researchers understand that because the cancer cells reproduce more quickly and uncontrollably than the healthy cells, an antifolate that interferes with cell reproduction could hit the cancer cells harder and spare the healthy cells.

In this difference between how the antifolates impact cancer cells and healthy cells is what allows the antifolates to treat cancer. Doctors and researchers also understand this folate pathway and how the antifolates work. They know that the antifolate competes with the natural folate, competes with -- competes as a different key to get into the lock, and so there was a theoretical understanding that the amount of functional folate in the cells could impact the result obtained with an antifolate. The fundamental takeaway, the evidence will show, is this: The whole idea of

antifolates is that they can have a differential effect on cancer cells and healthy cells, but exactly how and where that's going to happen is going to take some research.

The parties describe some of these theoretical issues during the tutorial, but those theoretical issues are going to be just part of the story. Here, the prior art goes well beyond the theory into actual research and study of pemetrexed. And that evidence will tell a person -- would tell a person of ordinary skill in the art that the claims here are obvious.

So what would a person of ordinary skill have known about pemetrexed in particular? They would know it was the most promising antifolate being researched in 1999. It had gone through preclinical animal studies to Phase 1 studies, to Phase 2 studies, and it was beginning phase three studies.

As we talked about this morning already, drug development often begins in these preclinical animal experiments. And here, in antifolate chemotherapy, there was a standard animal model that Lilly had developed using mice. In fact, the model is so standard, the '209 patent itself calls this model standard.

We have a publication by John Worzalla and others at Lilly. It is Trial Exhibit 384, and I'll leave it to the experts to explain exactly how they did this study and

precisely what the data showed. But the conclusion as set forth in this prior art publication about pemetrexed and folic acid, because in this animal study they gave folic acid, along with pemetrexed, needs little explanation.

The conclusion right in the abstract is folic acid supplementation was demonstrated to preserve the antitumor activity of pemetrexed while reducing toxicity, and you will hear a number of names for pemetrexed throughout the case. One of them is LY231514. That was Lilly's internal designation for the compound.

There will be evidence that this is how Lilly interpreted this data during the relevant time. When Lilly sought to add vitamin B12 and folic acid to pemetrexed during clinical trials, they explained why they should be allowed to do so to the FDA, and Lilly cited and interpreted some of the very same prior art references that the defendants are relying on now in that exchange with the FDA. And when they read those papers, when they told the FDA, if you read the research, this is what it will say, they said what we say it says.

Now, one example is that this very paper from John Worzalla and others at Lilly, Lilly presented this to the FDA in 2000, and what did they tell them? They specifically cited Worzalla, et al. 98. You can see that near the top of the slide in a discussion of cancer preclinical data, and they

said at the very end, "these data support the hypothesis that folic acid supplementation can protect healthy tissue from the toxic effects of pemetrexed with retention of antitumor activity." So adding folic acid to pemetrexed has this differential effect. It protects the healthy cells and lets pemetrexed continue to kill the cancer cells.

The evidence in the prior art concerning pemetrexed isn't limited to animal studies. There are also publications about giving pemetrexed to cancer patients. Prior art contains two abstracts published with the lead author Clet Niyikiza, who is the sole named inventor of the '209 patent.

These two abstracts, they will be Trial Exhibits 910 and part of 911, were presented at two major cancer conferences in 1998. At those conferences, Dr. Niyikiza explained that there was a correlation, a relationship between homocysteine, high levels of homocysteine and toxicity from pemetrexed.

The experts will again explain these publications, but the conclusions are worth noting. The bottom pullout here, the conclusion was that elevated baseline homocysteine levels greater than or equal to ten micro molars, highly correlate with severe hematologic and nonhematologic toxicities following treatment with MTA. MTA stood for multitargeted antifolate and was another name that Lilly had for pemetrexed.

In other words, patients who have high levels of homocysteine in their blood which can result from an inadequate nutritional status, and that's what they said in the beginning of this abstract, that they were looking at nutritional status, are more likely to have toxicity from pemetrexed. So that's in the prior art, too. Lilly's published the relationship between high levels of homocysteine and toxicity with pemetrexed.

The available information -- now these patients didn't receive folic acid, but there was a clinical trial that was also published in the prior art with pemetrexed and pretreatment with folic acid, like the Worzalla mouse study they gave folic acid before pemetrexed. Those are referred to in the case as the Hammond abstracts, after the first named author, Lisa Hammond. And those two abstracts were presented at the same major conferences in 1998 as the Niyikiza abstracts, this major American conference and major European conference that Niyikiza and Hammond research are both presented.

And one of the abstracts actually explains that this research was done because of the results in the Worzalla study. As preclinical evaluations indicate that folic acid supplementation increases the therapeutic index of pemetrexed, this study was initiated, so they go from the preclinical model to humans, as most people do. You see a promising

result in preclinicals, you move on to human studies.

The positive result of this study is plain on its face. As stated in Trial Exhibit 911, the conclusion was folic acid supplementation appears to permit pemetrexed dose escalation by ameliorating toxicity. Reducing toxicity with pemetrexed is a good thing, and that's what folic acid did here.

Now, this Hammond study is a Phase 1 clinical trial. As the parties explained during the joint tutorial, this is the first type of study with human beings. Dr. Ratain will explain the purpose is mainly to find a safe dose schedule for the drug. Very sick patients, usually who tried other cancer treatments and failed, were ineffective, take part in these trials. And they all have different types of cancer. There's no requirement in a Phase 1 that it only be people with breast cancer or lung cancer, pancreatic cancer, it's all kinds of cancer, because all we're looking for is there a safe dose?

They don't focus on how well the drug actually works because the patients are very sick, they've had very -- they have different kinds of cancer. They've had different treatments ahead of time, but the patients are sick, as we talked about. And so one of the Hammond abstracts includes an important signal for this case.

Trial Exhibit 912, they reported that there was one

partial response in a patient with metastatic colon cancer has been observed. That means at least one patient who was very, very sick had metastatic colon cancer, so it started in the colon and it spread beyond that, got at least a little bit better with this dose of folic acid and pemetrexed. And the evidence will be that this type of response is clearly a therapeutic benefit as contemplated by the construction of the claims.

So where would this leave the hypothetical person of ordinary skill in the art? They would know the theory behind antifolates and the folate pathway. They would understand that high levels of homocysteine in the blood before -- of a patient before they received pemetrexed means they are more likely to have toxicity. It is seen that Lilly has pretreated patients with folic acid and that it's reduced toxicity. They've seen they have even done that in a Phase 1 clinical trial, and there are some patients who received a therapeutic benefit from that.

Now, a person of ordinary skill in the art would also know how to reduce homocysteine levels in the blood of a patient. Dr. Green, who studied this for 30 or 40 years, will explain that the prior art is literally chock-full of publications on this subject. How do you lower homocysteine? And not surprisingly, based on the folate pathway as we talked about, the prior art suggests you give two things. You give

folic acid, and you give vitamin B12. The Court will hear about a number of these references from Dr. Green. Let me talk briefly about one example here.

The Ubbink article from 1994 is prior art. It will be Trial Exhibit 1446, and the very first sentence of the abstract sums it up. "We have previously shown that a modest vitamin supplement containing folic acid, vitamin B12, and vitamin B6 is effective in reducing elevated plasma homocysteine concentrations." And what does Ubbink mean by "a modest vitamin supplement"? The evidence will be that this is exactly the doses that are claimed by Lilly in the dependent claims that they are now asserting. I want to pause on this dosing issue for one more moment on another reference, which is the Lilly patent I mentioned before.

The '974 patent will be Trial Exhibit 916 and is an expired patent assigned to Lilly. It discloses and claims administering certain antifolates with folic acid pretreatment. Lilly may be arguing in this case that the patent is not directed specifically to pemetrexed, although I think they admit that it covers pemetrexed. And they told the FDA, as part of this Hatch-Waxman process, that the '974 patent covered pemetrexed.

What happens under the Hatch-Waxman Act is the brand company has to identify patents that are associated with and that cover a drug, and Trial Exhibit 1386 will be Lilly's

letter to the FDA in 2004, identifying patents for pemetrexed. You can see we have pulled out and identified the patent.

Question 4.2 is: What patent claim are you talking about? It's Claim 20, they say here, which is one of the claims we'll rely on.

The next question is: Does the patent claim referenced in 4.2 claim that approved method of the use of the approved product? They've checked yes, so they've sworn to the FDA the '974 patent covers pemetrexed. And just to be certain about it, in 4.2A, they've described what's called the "use code," which they've said, "to reduce toxicity, patients treated with Alimta" -- that's pemetrexed -- "must be instructed to take a low dose oral folic acid preparation or multivitamin with folic acid on a daily basis."

So there's really no question that the '974 patent covers pemetrexed, and it's also got basically the same schedule as they have claimed here. The patent will show you the '974 explains that you can give oral administration of folic acid for periods up to weeks before treatment of the active agent.

So let's turn, then, to the differences between the claimed subject matter and the prior art, the second of the gram factors. Obviousness doesn't require, as I said before, that all of the elements be present in one reference. The question is: What's the difference between the reference and

the prior art? And here the evidence will be not very much.

The only real difference is adding vitamin B12, and that was disclosed in the -- the prior art explicitly disclosed giving folic acid before the pemetrexed in the Worzalla and Hammond papers, and the difference is simply adding B12. The prior art we've already reviewed shows that when confronted with this folic acid pretreatment and the correlation with homocysteine, the first thing a person of ordinary skill in the art would do was add B12. That was the standard way to treat high levels of homocysteine.

Now, during the tutorial, the Court also heard about a second marker in patients, methylmalonic acid. The prior art as a whole will show that a person of ordinary skill in the art did not give vitamin B12 only when they saw a proven relationship or a proven elevated level of methylmalonic acid. Rather, when homocysteine levels were elevated, a person of ordinary skill in the art gives folic acid and B12 to make sure they have the best chance of reducing the homocysteine levels.

And that logic is exactly what Lilly used with the FDA. When they explained to the FDA they wanted to add both folic acid and vitamin B12, they didn't point to MMA levels; they pointed to homocysteine levels. In 1999, Lilly submitted a safety analysis to the FDA -- it will be Trial Exhibit 75 -- and they wrote, as mentioned in the introduction, "Elevated

homocysteine may also be caused by vitamin B12 deficiency in a small percentage of patients."

There's another reason you will hear about during trial about why a person of ordinary skill in the art would add vitamin B12 with folic acid. It will be referred to as masking. The problem that happens is that patients who have a folic acid deficiency exhibit certain symptoms, and the people with B12 deficiency exhibit some of the same symptoms. If you give only folic acid, you can mask or hide the B12 deficiency and cause irreversible nerve damage that comes from the actual underlying B12 deficiency.

And a person of ordinary skill in the art would reasonably expect that the combination of folic acid and vitamin B12 pretreatment together with pemetrexed would result in a therapeutic benefit. Why? For the same reason that the folic acid seemed to be working, as Worzalla and Hammond and the Hammond references show, you can change the balance between efficacy and toxicity by increasing functional folate in the healthy cells by giving folic acid. When a person of ordinary skill in the art knows the folic acid is okay to give, adding the B12 won't change anything.

Let me turn to the third of the Graham factors, the skill level of a person of ordinary skill in the art. Usually, there's not much of a dispute about this, and Your Honor already addressed this issue in claim construction. The

Court concluded that a person of ordinary skill in the art can be a medical doctor who specializes in oncology or a medical doctor with extensive experience in the areas of nutritional sciences involving vitamin deficiencies, but that person should work with an oncologist.

The defendants agree with that definition. The patent supports it. The prior art identifies the nutrition issues. But the plaintiffs are still fighting against it. Why? Another expert for the defendants will be Dr. Sarah Morgan. She's not an oncologist; she's an expert in nutrition who published research concerning methotrexate, another antifolate with folic acid. And she established in the '90s in the prior art that giving folic acid with methotrexate didn't diminish the efficacy. And she also observed that if patients were B12-deficient, explicitly in her articles, then you should give them B12 to avoid the masking concern. So she's going to come in here and explain as a witness the research she did and why at the time there was no concern about giving folic acid and vitamin B12 with an antifolate.

The last point I'll make about this is that Lilly may argue that the nutrition literature and Dr. Morgan's literature are irrelevant to the case because they're not about cancer, but the best evidence that that's not true is the Worzalla paper itself, published by Lilly in a journal called *Anticancer Research*, and citing, as you see here,

Morgan and co-workers, number ten. Slide 30 is Dr. Morgan's work.

Let me turn to the last of the Graham factors, secondary indicia of non-obviousness. Here, defendants will present in their rebuttal case, not up front but after plaintiffs go, evidence that the secondary considerations are irrelevant. As we set forth in our motions in limine, the plaintiffs will be unable to establish a nexus, any connection between the new part of the invention, which is just vitamin B12, and the commercial success or unexpected results or positive results of the combination.

What happened here is that although a person of ordinary skill in the art would be motivated to add B12 because some patients might need it to lower their homocysteine, it turns out it really doesn't do very much. It's the folic acid that's already in the prior art that really leads to the benefit. So no sales or results are in turn driven by the invention here of adding B12.

The other issue, as we flagged in the motions, is that Lilly had other patents, and when there are other patents out there that prevent commercial development by others, there's not an incentive to develop the product. So the failure of others to develop it, even if there was money to be made, is not really probative of the obviousness or non-obviousness of the patent.

Let me turn, then, to the separate defense of obviousness-type double patenting, which is based on the '974. We can actually win this one even if we lose obviousness. They're independent defenses. And you'll hear from Dr. Ratain about this defense, as well.

As a matter of law, this defense begins with the claims of the '974 patent. We've put claims 15 through 20 up on the screen. Simply put, the claims require giving a certain kind of antifolate and -- giving folic acid before a certain kind of antifolate to reduce toxicity. And the evidence will be that pemetrexed is this certain kind of antifolate, and folic acid in the doses here is the same dose as the '209 patent.

Now, admittedly, the schedule in claim 19 is slightly different; it's one to 24 hours in advance of the antifolate, and not one to three weeks as required by some of the asserted claims, but the '974 patent specifically says that doesn't matter. It says you can give the patent -- you can give the drug -- the folic acid one to 24 hours in advance or in column six you can give it up to weeks in advance, just like they claimed in the '209 patent.

Where does that end up leaving us with this argument? Exactly the same place with obviousness in the end. We have an antifolate, including pemetrexed, with folic acid. Would it be obvious to add vitamin B12? The evidence, we

suggest, will lead to the conclusion that it would.

Let me turn, then, to the other defenses that will be presented for a few minutes, but before I do, I want to talk about the relationship between the two sets of the defenses. The sets of defenses, the prior art defenses I've already talked about on one hand and these failure-to-disclose-in-the-specification defenses we're about to talk about are basically offered in the alternative. In trying to defend against the prior art defense, Lilly is contending that the effects of that in folic acid and B12 to pemetrexed are so unpredictable a person of ordinary skill in the art wouldn't be able to figure out how to do it. But in defending against these failure-to-disclose defenses, they're saying, "Well, yeah, we don't really disclose the dose and schedule of pemetrexed, but a person of ordinary skill in the art could figure out how to do it." Those positions are fundamentally inconsistent. That's a problem for them.

Now, for us, either way, the patent is invalid. We can present arguments in the alternative, and for you, if the Court finds that the person of ordinary skill in the art could figure out the dose and schedule of vitamin B12 and folic acid to work with pemetrexed, the claims are obvious. And if you -- if the Court finds that a person of ordinary skill in the art couldn't figure it out, the claims are invalid for failure to disclose that information. One or the other, but

either way, the patents are invalid.

Now let's turn to those defenses briefly. They're grouped under 35 U.S.C. Section 112. And you will hear from Dr. Thomas Schulz on behalf of defendants. Dr. Schulz is the doctor who's most prescribed pemetrexed of, I think, anybody who will testify here, and he will explain the defenses concerning the written description, the lack of enablement and the failure to disclose the best mode. The focus of this will be on what is the disclosure of the dosing schedule of pemetrexed in the '209 patent.

And there's only -- there's no dispute there's only one dosing schedule for an antifolate disclosed. It's in column eight, lines 46 to 54. The antifolate is administered in four doses over a two-week period by rapid intravenous injection followed by two weeks of nontherapy. Dosing is made on days one, four, eight and 11 of any two-week period. Patients will have an initial course of therapy at a dose of five milligrams per meter squared per dose.

There's no question that this is not the dose of pemetrexed that Lilly was using when they filed the application in June of 2000. In order to maintain a monopoly by getting a patent, the statute requires that you teach -- you disclose the invention, you teach people how to make it, and if you have a best way of doing it, you disclose that. That makes sense in exchange for the 17-year monopoly. You're

not supposed to disclose a mediocre way or not quite how to do it in exchange for a monopoly.

Here the evidence will be that the sole named inventor, Dr. Niyikiza, was involved in developing and analyzing clinical trial results. He knew the dosing schedule being used was nowhere near the regimen that's in the patent for the antifolate. Instead, Lilly was dosing pemetrexed once every three weeks, not four times every two weeks, at 500 milligrams per meter squared, more than 100 times the amount of pemetrexed at a time and more than 25 times the amount of pemetrexed over a month-long period.

Although the '209 patent actually looks like it includes a lot of portions straight out of the clinical trial that was being run, the details about how to dose pemetrexed itself, part of the claims, was nowhere to be found. Now, Dr. Niyikiza may be here and may testify that he didn't really have a preference for what dosing schedule was used, but the contemporaneous evidence will show he was part of the team that decided on this as the dosing schedule at the time back in 1999 and 2000.

Let me conclude for a few minutes with what we expect to hear from Lilly during this case. First, we expect to hear that a person of ordinary skill in the art would be worried that giving folic acid and/or vitamin B12 with pemetrexed would undermine or eliminate the efficacy of the

drug; it wouldn't work as well to treat cancer. The evidence will probably be that this was a theoretical concern based on the folate pathway and the understanding of how the enzymes work.

But in the mind of a person of ordinary skill in the art, that theoretical concern was alleviated by the actual publications with pemetrexed. They'd know that there was a target spot, a sweet spot, that could be obtained where folic acid and B12 could be used to protect the healthy cells while still allow -- or, yeah, to protect the healthy cells while still allowing pemetrexed to kill the cancer cells, just like Lilly itself demonstrated was possible in their mouse model in the Worzalla case.

Second, Lilly may argue that a person of ordinary skill in the art would, in fact, not want to give vitamin B12 because it could actually cause a tumor to grow. So if you give it to cancer patients, that would be a bad idea. We're going to ask you to look carefully at the evidence because it's weak at best, and when considered as part of the entire record, as part of the prior art as a whole, the evidence will not support the conclusion that a person of ordinary skill in the art would be concerned that vitamin B12 would cause tumor growth. It's actually contrary to the very things that Lilly did back in 1999 and 2000 and contrary to what Lilly told the FDA.

Another document, if I can get this back up -- there we go -- that we'll see is a March 1 -- is meeting minutes that Lilly sent to the FDA on March of -- in March of 2000. It's Trial Exhibit 337. At this point, Lilly is going back and forth with the FDA about whether to amend their clinical trial protocol to add folic acid and vitamin B12. And the subject comes up, is vitamin B12 a problem because it will cause tumors to grow? What does Lilly tell the FDA? "For vitamin B12, literature searches found no evidence for stimulation of tumor growth by this vitamin."

Third, we expect Lilly is going to argue that there were conventional ways to deal with toxicity from pemetrexed. Lilly doesn't deny there was some toxicity with pemetrexed. It's true with most chemotherapy drugs, and there still is even with vitamin supplementation. We expect Lilly will argue a person of ordinary skill would merely adjust the dose or the schedule of pemetrexed to deal with the toxicity.

The evidence will show that this adjustment would create exactly the problem Lilly says that a person of ordinary skill in the art would be concerned about: It will decrease the efficacy just the same way it decreases toxicity. There's no evidence that there's any differential effect from decreasing the dose or schedule between the healthy cells and the cancer cells. The only evidence you will hear in the case about a differential effect is that adding folic acid and B12

as it related to folic acid in making active folates available is the best way to have a differential effect sparing healthy cells or killing cancer cells.

Finally, Lilly will look at the disclosure of the patent and ask you to find that it's sufficient. They may point to some prior art that's cited in it. They may argue that a person of ordinary skill in the art could figure out how to use pemetrexed with the invention. But as I explained, that will be insufficient to save the patent.

Fundamentally, Lilly is going to ask you to listen to their lawyers and experts in this case and accept the arguments they're making today. They'll ask the Court to look at each reference one at a time, and they'll ignore or discredit or attack their own research from the past. They'll give the Court excuses for what they told the FDA in the past and why it's not inconsistent with what they're arguing today.

But the patent statute instructs you to look at the prior art as a whole. It doesn't require any particular reference to be perfect, or that a person of ordinary skill in the art would be absolutely assured of success.

The defendants will ask you to look at the prior art as a whole, as a person of ordinary skill in the art would analyze it, and to conclude that the patent-in-suit is invalid. Thank you.

THE COURT: Thank you. Do you want to take a break

before you get started?

MR. PERLMAN: Whatever you prefer, Your Honor.

THE COURT: I'm fine.

MR. WIESEN: I'm fine.

THE COURT: Are you ready? Come on.

MR. PERLMAN: I'm ready. I have some materials that I'm going to be showing.

THE COURT: You may, Counsel.

MR. PERLMAN: Thank you, Your Honor.

The key to this case, the things scientists were focused on, the things scientists were worried about was making sure you don't hurt the efficacy of this very promising cancer drug.

In the second half of the 1990s, pemetrexed looked very promising. You just heard Mr. Wiesen say it. The literature reported that it had shown efficacy in treating a large number of different kinds of cancer, ranging from colorectal cancer to lung cancer to mesothelioma and more.

At the same time, the literature reported that the toxicities that the drug caused were generally manageable and tolerable. Like all chemotherapy agents, pemetrexed did cause some serious toxicities in some patients. And a Lilly scientist named Clet Niyikiza, who will testify in this case, came up with an idea for how to protect patients from these side effects.

His idea was that if patients were given both vitamin B12 and low levels of folic acid before they were given pemetrexed, this could reduce or eliminate the most serious toxicities associated with the drug without undermining the drug's efficacy in treating cancer.

Let me show you Claim 12 of the '209 patent, which is a representative example of Dr. Niyikiza's invention. There is no dispute that the defendants infringed this claim and the others that Lilly has asserted.

As you can see, the claim is to an improved method of administering pemetrexed disodium to a patient in need of chemotherapy. Pemetrexed disodium is the form of pemetrexed in Lilly's product and in the defendant's products. And the improved way of giving pemetrexed is giving both about 350 to about a thousand micrograms of folic acid, and about 500 to 1,500 micrograms of vitamin B12 before giving the patient pemetrexed.

The evidence will show that Dr. Niyikiza's idea went against the conventional thinking. In June 1999, scientists thought that pretreating patients receiving an antifolate with folic acid and vitamin B12 would reduce the antifolate's ability to treat cancer.

And there are two principal reasons for that: First, tumors use these vitamins to grow, and giving patients more of the vitamins could cause the tumor to grow more.

That's not to say that doctors thought cancer patients should be starved of these vitamins. Some amounts of folic acid and vitamin B12 are part of a normal diet, and cancer patients were generally told that they should try to eat a normal diet. But, what doctors would not have wanted to have patients consume the amount of folic acid and vitamin B12 that they would get as part of a normal diet and then, in addition, give them even more of these vitamins before starting the cancer therapy.

Pretreating patients with folic acid and vitamin B12 also would have been expected to reduce the antitumor effect of pemetrexed. As I told you a few minutes ago, pemetrexed is an antifolate. There is a competition within the body between folates and antifolates for access to the enzymes that use folates.

Giving a patient folic acid and vitamin B12 increases the amount of folate available to compete with the antifolate, and therefore makes it harder for the antifolate to do its job, to be effective. The expectation among scientists, therefore, was that pretreating a patient with folic acid and vitamin B12 would reduce the efficacy of pemetrexed.

Your Honor, this is going to be an unusual obviousness case. In the usual case, you would hear testimony from each side's expert today about whether the invention

would have been obvious years before when the patent was filed, and you're going to get that, too, in this case.

But, in this case you will also hear contemporaneous evidence that Dr. Niyikiza's idea met with significant resistance inside Lilly, among the expert scientific advisors Lilly retained to help it, and from the FDA. Lilly had many of the best oncologists in the world advising it on the development of pemetrexed, and the evidence will show that they repeatedly recommended against Dr. Niyikiza's idea because they were concerned that it would reduce the efficacy of pemetrexed.

The FDA expressed the same concern. In 1998, Lilly submitted to the FDA two clinical trial protocols that contemplated giving patients folic acid, vitamin B12, and vitamin B6 before giving them pemetrexed. In response, just like Lilly's consultants, the FDA expressed concern about the effect of giving vitamins on pemetrexed's efficacy after which Lilly took the vitamins out of the protocol because of that concern.

The expectation that vitamin pretreatment would hurt pemetrexed's efficacy would have been a grave concern in June 1999. That is because pemetrexed was showing great promise in its ability to treat multiple kinds of cancer. And while it had shown the ability to cause serious toxicities in some patients, its toxicities were, by and large, tolerable and

manageable.

It is important to remember here, Your Honor, that all chemotherapy drugs cause serious toxicity. We all know that from our life experiences, but because cancer is such a serious and difficult to treat disease, doctors and patients are willing to tolerate a significant amount of toxicity in order to be able to use a drug that has the potential to treat a patient's cancer, far more than you'd accept in other contexts. And doctors do not want to do anything that will undermine the efficacy of the chemotherapy to fight this deadly disease unless they have no choice.

In late 1999, after the June 1999 date that's relevant for the defendant's obviousness case, the calculus here changed dramatically. Lilly had begun a large-scale global clinical trial of pemetrexed for treating mesothelioma, which is a cancer caused by asbestos, which you may have heard of.

In the early parts of this clinical trial, there were an unacceptably high number of drug-related deaths. Upon realizing this was happening, Lilly undertook a crash project to try to figure out what to do. And ultimately, in December 1999, because of the concern for patients' safety, Lilly decided to implement Dr. Niyikiza's folic acid and vitamin pretreatment regimen.

Lilly and its expert consultants were still worried

that this risked hurting the efficacy of the drug, but given the risk to patients that had emerged, they felt they had no choice but to take that risk.

The FDA's initial reaction to Lilly's plan was again negative as it continued to believe that adding vitamins would risk the drug's efficacy. Through a series of submissions, Lilly tried to convince the FDA to allow it to try Dr. Niyikiza's regimen.

You heard in the opening, and you're going to hear in this trial, the defendants talk about what Lilly told the FDA in these submissions as if it is some evidence of what the person of ordinary skill in the art would have thought in June 1999.

The critical points to remember about this are that these submissions were put together by people who already knew Dr. Niyikiza's invention, and who faced a very different situation in terms of the expected toxicity of the drug than what was publicly known in June 1999.

That is the exact opposite of the person of ordinary skill, who considers only what is known in the prior art without using the inventor's own invention as a blueprint to know what to go focus on in hindsight.

And perhaps most telling, Your Honor, even after reviewing Lilly's submissions, the FDA still remained unconvinced that Lilly should do this. Ultimately, the

Lilly -- the FDA agreed that Lilly could proceed at its own risk despite the FDA's concerns. And Lilly did it and it proved to be a resounding success. The incidence of severe toxicities and death decreased unexpectedly without harming the drug's efficacy.

Pemetrexed went on to be approved for the treatment of mesothelioma, becoming the first drug ever approved to be approved for treatment of that disease, and it's also been approved to treat the most common types of lung cancer.

Pemetrexed has now been used by almost one million patients, and its cancer-fighting ability has made pemetrexed, which Lilly sells under the name Alimta, an extraordinarily successful product for Lilly, generating billions of dollars in sales, and making it Lilly's second largest-selling product worldwide.

The defendant's position is that notwithstanding all of the resistance that Dr. Niyikiza faced to his idea from the experts and consultants, from Lilly, from the FDA, his invention was actually obvious. They say this despite the fact that in the 50 years that antifolates have been used, there is not a single example in the literature of anyone pretreating any cancer patient with both folic acid and vitamin B12 prior to giving them an antifolate or suggesting that this would be desirable to do.

While there are isolated examples of pretreating

cancer patients with folic acid, none of these examples used vitamin B12 or even discussed the possibility of using it.

As you listen to the evidence, ask yourself, if it was really obvious to pretreat antifolate cancer patients with vitamin B12, wouldn't you expect that in 50 years, somebody would have done it or at least published that they thought it was a good idea? The evidence will show that they did not because it was not obvious.

The defendants start their obviousness case with the proposition that the person of ordinary skill would have been motivated to give cancer patients folic acid before giving them pemetrexed in an attempt to lower the toxicities that had been seen with the drug. The evidence will show that the person of ordinary skill would not have done this, because they would have thought that it would have reduced the very promising efficacy that the drug had shown.

In fact, the person of ordinary skill would have thought that any amount of folic acid that could lower the drug's toxicity, that would be useful for doing that, would also lower the drug's efficacy. And the reason for that, as you saw in the tutorial, is that pemetrexed's toxicity and its efficacy against cancer, both come from pemetrexed's ability to prevent cells from dividing and growing.

This effect is beneficial when it comes to cancer cells and leads to the drug's anti-cancer efficacy. The same

mechanism, though, also prevents certain healthy cells from dividing and growing, which leads to toxicity for the patients. Giving a folate like folic acid can counteract the side effects, but it was understood in 1999 that doing so would similarly counteract an antifolate's desirable effect on cancer cells.

The evidence in the prior art about giving folic acid before giving pemetrexed confirmed the person of ordinary skill's expectation that doing so would reduce the efficacy of pemetrexed.

The only published testing of using folic acid with pemetrexed in humans before June 1999 is reported in the Hammond abstracts, which I put excerpts of up on the screen.

Both abstracts are about the same Phase 1 study in which patients were given five milligrams of folic acid for five days, starting two days before they received pemetrexed, and the results were discouraging. As you can see on the slide, out of 33 patients total, there was only one partial response to the drug.

By way of comparison, as you can see here, another Phase 1 study of pemetrexed without folic acid yielded four partial responses and six minor responses among 37 patients, a difference that is made all the more striking by the fact that Hammond used higher doses of pemetrexed.

Mr. Wiesen talked about comparing Phase 1 trials.

The evidence will show that to the person of ordinary skill, the Hammond abstracts confirmed the skilled person's expectation that giving folic acid would reduce the efficacy of pemetrexed.

Your Honor, the parties take away very different messages from Hammond. We look at the one partial response reported in Hammond in comparison to other studies and say that this shows pemetrexed's efficacy was reduced compared to trials without folic acid.

The defendants focus on that same single partial response, and say that that means pemetrexed's efficacy was retained. And what they mean by "retained" is it was not completely eliminated. And because it wasn't completely eliminated, they say that the person of ordinary skill would have expected from Hammond that even if the patients were pretreated with folic acid, pemetrexed would still be capable of providing some therapeutic benefit to some patient, which is what the phrase "effective amount of pemetrexed" in Lilly's patent claims has been construed to require.

We are not suggesting that the skilled person would have expected that using folic acid pretreatment would make pemetrexed completely inactive and useless, but that is not the issue, Your Honor.

The question for obviousness is whether the person of ordinary skill would have been motivated to pretreat

pemetrexed patients with folic acid when they thought that doing so would significantly reduce the efficacy of the drug.

The evidence will show that they would not have been. The patients who would be treated with pemetrexed had serious, generally life-threatening diseases. Pemetrexed had been shown to have very promising activity against these terrible diseases with tolerable and manageable toxicity.

The person of ordinary skill would not have wanted to dilute the efficacy of pemetrexed in combating patients' cancers, which is what Hammond thought folic acid pretreatment would do. Hammond, therefore, would have been seen as a step in the wrong direction. The fact that Hammond, the Hammond regimen, did not completely eliminate the drug's activity did not provide any reason for the person of ordinary skill to want to pursue that regimen.

The only other report in the prior art of using folic acid with pemetrexed is the Worzalla article that Mr. Wiesen talked about. Worzalla did not perform any testing in humans. Rather, the article reports on testing in mice and on some cell cultures in test tubes. And what Worzalla showed was exactly what the skilled person would have expected, that the addition of folic acid reduced the activity of pemetrexed.

What Worzalla found was that to get the same level of activity in the presence of folic acid, you needed to use 100 times more pemetrexed.

This is Figure 2 from Worzalla. Let me walk you through this. This is in mice, who had been fed a low folate diet because the regular mouse chow has a lot of folate in it.

Across the bottom of the graph is the dosage of pemetrexed. Along the side is the percent inhibition of the tumors, with zero at the bottom and 100 percent inhibition at the top.

The circles, which I've highlighted in yellow, shows how much tumor inhibition you get with different amounts of pemetrexed in mice who were not given supplemental folic acid. You see it's way over to the left.

The triangles, which I've highlighted in green, show the same thing, but this time for mice that were given folic acid supplementation. And that's way over to the right now. As you can see, you need 100 times more pemetrexed to get the same effect if you give the mice folic acid because the folic acid is counteracting the pemetrexed.

And that's what the authors of Worzalla note in talking about this figure. They say "Oral folic acid preserved," or like the defendant would say, "retained antitumor activity, albeit at higher dose levels." That's the same take-away message as from Hammond. Pemetrexed's activity against tumors is not completely eliminated by folic acid, but it is dramatically reduced; here shown by the need to use much, much higher doses of pemetrexed to get the same effect.

Giving mice 100 times more pemetrexed was possible in Worzalla's experimental study in mice. There are things you can do in testing with mice you would never do with a person. A person of ordinary skill would have known, though, that in humans you couldn't simply raise the dose of pemetrexed to try to make up for the decrease in activity that pretreating with folic acid causes.

In Hammond, they raised the dose of pemetrexed to less than twice the level, not a hundred times, less than twice the level it was in previous studies, and the results suggested that at these higher doses, what you got was toxicity to the kidneys.

That's not related to the antifolate effect. That's what's called an "off-target toxicity." As you give more drug, all kinds of things can happen, many of them bad. This would have been of great concern to the person of ordinary skill, and is another reason the person of ordinary skill would not have pursued the Hammond regimen.

Hammond and Worzalla are the only references that the defendant relies on that are about administering folic acid with pemetrexed. Both of them showed that when you do that, the drug's efficacy is reduced.

You are going to hear about a number of other references in this case, but the key point, Your Honor, is that none of them would have assuaged the person of ordinary

skill's concern that giving folic acid before giving pemetrexed would reduce the efficacy of the pemetrexed.

You heard already, and you're going to hear during the trial, about two abstracts that Dr. Niyikiza published in 1998 describing early versions of a statistical analysis that he performed called the multivariate analysis, and he'll tell you what's involved in that.

In this analysis, he found that patients who had certain levels of homocysteine before they started taking pemetrexed were more likely to have certain toxicities. But here's the point. The point of the Niyikiza abstracts was to identify characteristics of the patients who suffered severe toxicities.

The abstracts do not propose a solution to this toxicity problem, let alone suggest that pretreating patients with vitamins is the solution. And more fundamentally, there is nothing in the Niyikiza abstracts that suggests that you can give folic acid to pemetrexed patients to reduce toxicity without reducing the efficacy of the drug, which is what you wouldn't have wanted to do.

Let's talk about the '974 patent, which you've heard about already, and I expect you're going to hear repeatedly -- it started this morning already -- over the course of this trial that before the '209 patent, Lilly had another patent called the '974 patent that covered the use of folic acid with

pemetrexed. You'll hear it as part of the obviousness case, and you'll hear it as part of the double patenting defense.

This is Claim 16 of the '974 patent. It generically covers administering folic acid prior to administering a broad class of antifolates. Pemetrexed is one of the myriad antifolates that falls within this class, and so the defendants are correct that the '974 patent protected Lilly's commercial pemetrexed product, and we told the FDA it did because it does, or it did before it expired.

The relevant question for this case, though, is whether the '974 patent would have motivated the person of ordinary skill to pretreat pemetrexed patients with folic acid. And it would not have. Nothing in the '974 patent would have overcome the person of ordinary skill's concern that giving folic acid before giving pemetrexed would reduce the efficacy of the drug.

In fact, the skilled person reading the '974 patent would not have focused on pemetrexed. The '974 patent never mentions pemetrexed either by name or by chemical structure. It doesn't have any data on pemetrexed. And it's not addressed to pemetrexed in particular.

The drug that the skilled person would have focused on in the '974 patent was lometrexol, which was an earlier antifolate that Lilly was working on that ultimately failed and never reached the market.

By June 1999, there had been clinical testing. This is just a patent. By 1999, there had been clinical testing of lometrexol in combination with folic acid, and you know what? The results were just what the person of ordinary skill would have expected. When folic acid was administered, lometrexol's efficacy was significantly reduced.

And so in 1999, whatever snippet from the '974 patent Mr. Wiesen put up on the screen, the person of ordinary skill would have understood that when you gave folic acid with lometrexol, which is the suggestion, it didn't work. It made the efficacy worse. Not reduced the toxicity. Of course, it did, but it made the efficacy worse. And that drug failed.

The evidence will also show that the only two antifolates approved for cancer treatment in the United States or Europe in June 1999, which are drugs called methotrexate and raltitrexed, both of them had labels warning people against using folic acid in combination with the drug because it could reduce the drug's anti-cancer efficacy, and you'll see that in evidence.

Now, Mr. Wiesen talked about Dr. Morgan and her work on rheumatoid arthritis. You're going to hear evidence in this case about how methotrexate, which is used to treat cancer is also used to treat rheumatoid arthritis, which is an entirely different disease from cancer. And what you will

hear is that in rheumatoid arthritis patients, folic acid reduces the toxicities associated with methotrexate, but it does not impair its efficacy in treating rheumatoid arthritis. But there's a critical distinction to bear in mind, Your Honor, when you hear this evidence.

When methotrexate is used to treat cancer, its efficacy and toxicity are caused by the same mechanism, the antifolate mechanism that causes it to prevent cells from dividing and growing. Giving folic acid can reduce the toxicity, but at the same time, it will reduce the efficacy of the drug.

When the drug is used to treat rheumatoid arthritis, its efficacy and toxicity are caused by different mechanisms. The toxicities are still caused by the antifolate mechanism preventing cells from dividing and growing, but the drug's efficacy is not. What that means is that for rheumatoid arthritis, giving folic acid can reduce the toxicity, but it will not undermine the efficacy. Very different from cancer.

This difference in mechanism is why in June 1999, even though folic acid was given when treating arthritis patients with methotrexate, folic acid pretreatment was not used when methotrexate was used to treat cancer, because doing so would have undermined the drug's anti-cancer efficacy.

That doesn't suggest using -- pretreating pemetrexed patients with folic acid. It suggests exactly the opposite:

Don't do it.

I want to now focus briefly, Your Honor, on two other aspects of Lilly's claims as they relate to the use of folic acid. The first thing is that every one of the claims that Lilly is asserting in this case requires the use of 350 to 1,000 micrograms of folic acid, or a narrower range. Recall that Hammond used at least five times as much as the upper end of this. Hammond used five milligrams, or 5,000 micrograms of folic acid. Quite a difference.

I expect what you're going to hear, Your Honor, is that the skilled person would have dialed back the amount of folic acid from the amount in Hammond, so as to try to reduce the adverse effect on efficacy, but the problem is, there's nothing in the prior art suggesting that if you do that and lower the dose, you'll still get the reduction in toxicity that you're going to hear is the whole reason to look to Hammond in the first place.

And there's nothing that tells you you're going to achieve your goal by using the particular amounts in Lilly's claims. Giving this amount of folic acid in the cardiovascular literature, no context was known, but there was nothing that said if you did that here, you could reduce toxicity of a cancer drug and also not harm the efficacy of the cancer drug.

The second aspect I want to highlight is Claim 19.

This claim requires administering folic acid one to three weeks before the administration of pemetrexed. Hammond, you recall, started folic acid two days before pemetrexed.

The evidence will show giving folic acid before you give the drug is potentially feeding the tumor, and the evidence will show that the person of ordinary skill would have been concerned that starting the folic acid supplementation even earlier than Hammond did would feed the tumor even more. And they would not have been motivated to extend the length of time of the pretreatment.

Let's now talk about vitamin B12, pretreating pemetrexed patients with vitamin B12. What you will hear from the defendants in this case are hindsight reconstructions of reasons why the person of ordinary skill would have wanted to pretreat cancer patients with vitamin B12 in June 1999.

For 50 years, scientists had been looking for ways to safely and effectively administer antifolates to treat cancer. And despite that, the evidence will show that for 50 years, no one gave cancer patients vitamin B12 before giving them an antifolate, which is powerful evidence that it was not obvious to do.

The closest the defendants are going to come to an example of someone giving a cancer patient vitamin B12 in connection with giving them an antifolate is an article by Farber from 1948. But Farber didn't pretreat the patients

with vitamins and he didn't give them B12. What Farber did was giver liver extract to patients who were taking one of the first antifolates ever, something called "aminopterin" either simultaneously with the drug or after the patient had already received a dose of the drug.

Liver extract we now know contains vitamin B12 so the defendants call this administering vitamin B12. The evidence will show that the person of ordinary skill wouldn't have understood what Farber did to suggest pretreating patients with vitamin B12, but, Your Honor, even if it did, this is 1948. It was a suggestion that the art for five decades uniformly rejected. That is evidence it was not an obvious thing to do.

And Farber, by the way, published in *The New England Journal of Medicine*, not exactly a minor publication. In fact, the prior art cautioned against using vitamin B12 supplements in cancer patients because of the risk that giving more B12 to a patient could help the patient's tumor to grow.

This is the 1998 version of the ViDAL, which is a French medical reference that gives physicians prescribing information for approved drugs. You're going to hear the defendants call this a dictionary because the French word for this Dictionnaire ViDAL, we'd literally translate in English to dictionary, but what this is is a medical reference that French physicians look to for information about approved

products.

And look, it says a contraindication. It warns against giving vitamin B12 to patients with malignant tumors, which is cancer because it can cause the tumor to grow. You'll see other literature in this case that makes the same point, that vitamin B12 can stimulate tumor growth.

Mr. Wiesen put up in his opening statement that Lilly made to the FDA in the year 2000, well after the priority date, that they did searches and couldn't find evidence of this happening. All that means is the person doing the search didn't find it. Both the ViDAL and other references you will see are part of the relevant art. They warned against this. And what you're going to hear from the defendants is there are other references that don't say that.

But those references don't say "Go ahead, everything's fine." They're just silent on the subject. There's not going to be any evidence that the question was put to the authors. They're just silent.

The second point, Your Honor, is because of the role B12 plays in the folate pathway, the person of ordinary skill would have been concerned that pretreating pemetrexed patients with vitamin B12 could reduce the drug's efficacy, because, as we saw on the tutorial, giving more vitamin B12 could increase the amount of folate available in the cell to compete with the pemetrexed.

One rationale that you heard this morning and you're going to hear from the defendants for the use of vitamin B12, is that the Niyikiza abstracts showed that elevated homocysteine is correlated with toxicity and that it was known that both folic acid deficiency and vitamin B12 deficiency could cause elevated homocysteine. Here's one of the Niyikiza abstracts. In fact, the Niyikiza abstracts report that there was no correlation between toxicity and a host of factors, including levels of MMA, which you recall as a marker for vitamin B12 deficiency.

This would have led the person of ordinary skill to conclude that the patient's elevated homocysteine levels were not caused by a vitamin B12 deficiency. The person of ordinary skill, therefore, would have had no reason to give vitamin B12, particularly where there would be concern that doing so would have the down side effect of reducing the efficacy of the drug.

A lot of the nutritional literature you heard Mr. Wiesen talk about, about giving B12 and folic acid to patients, that's not about people with cancer. That's about making people generally healthier or eliminating a long-term cardiovascular risk. None of that literature says go ahead and do it and give it to a cancer patient if you think doing so is going to make it harder to treat the cancer.

The other rationale the defendants offer for

pretreating pemetrexed patients with vitamin B12 is that if you give folic acid without B12, you're going to mask the B12 deficiency. You heard a little bit about this in Mr. Wiesen's opening. What this is talking about, this is a theoretical concern that the initial clinical symptoms of a folic acid deficiency and a vitamin B12 deficiency are similar to each other, and so if you give folic acid, the symptoms are going to go away. But if the real underlying concern is actually a B12 deficiency, you won't have addressed it, and the patient could develop certain neurological symptoms later on. You're lulled into thinking you've handled the problem when you haven't.

The evidence will show that the possibility of masking a vitamin B12 deficiency would not have been a concern to the person of ordinary skill. Indeed, in the examples that the defendant cites of somebody giving a cancer patient folic acid before giving them an antifolate, no one ever gave the patients vitamin B12, and no one raised any concern about potentially masking a vitamin B12 deficiency. And that's perfectly understandable, because the evidence will show that developing neurological symptoms of a vitamin B12 deficiency is very rare. And on the occasions when it does happen, it generally takes a very long time to develop, far longer than the typical course of antifolate chemotherapy that would have been contemplated in 1999.

The person of ordinary skill would not have risked the efficacy of pemetrexed in treating a patient's serious and potentially life-threatening cancer simply to address the hypothetical possibility that they might have an unknown latent vitamin B12 deficiency, there would likely be ample time to address after the chemotherapy was completed. And perhaps the best evidence that masking a vitamin B12 deficiency would not have been a concern is the practice of giving folic acid to rheumatoid arthritis patients taking methotrexate, which you heard about.

These people are often on methotrexate for years to treat their arthritis, and they take folic acid every day to reduce the drug's toxicities. In fact, they take at least as much and generally more folic acid than the amounts in Lilly's claims. And yet, the evidence will show that it was not the practice to also give these patients vitamin B12.

If doctors were not worried that giving arthritis patients folic acid without vitamin B12 for years at a time would mask a vitamin B12 deficiency, they surely would not have given vitamin B12 to a pemetrexed patient who would only be receiving the same or a lower dose of folic acid for a much shorter period of time, particularly when giving B12 to the pemetrexed patient risks harming the efficacy of the chemotherapy.

What I have talked about up until now, Your Honor,

are reasons that the person of ordinary skill would not have been motivated to make Dr. Niyikiza's invention. The evidence will show that there are several objective indicia of non-obviousness, the fourth factor that you saw, which further show that Dr. Niyikiza's invention was not obvious. I am not going to talk about all of them here, but I do want to touch briefly on two of them.

The first is skepticism of others, which can be powerful evidence that an idea was not obvious. As we've already discussed, Lilly's expert consultants and the FDA repeatedly resisted the idea of pretreating pemetrexed patients with folic acid and vitamin B12 because they were concerned that it would reduce the efficacy of the drug.

You will also hear, Your Honor, that in 2004, long before he was ever retained by Lilly as an expert in this case, Dr. Bruce Chabner, who was clinical director of the cancer center at Massachusetts General Hospital, told the Wall Street Journal that when he heard about Lilly's vitamin supplementation plan for pemetrexed, "I thought it was crazy." And you will hear evidence that like Dr. Chabner, other oncologists were skeptical of Dr. Niyikiza's invention. Related to this evidence of skepticism is evidence that Dr. Niyikiza's invention possesses unexpected properties.

The reason that Dr. Chabner and others were skeptical is that pretreating patients with folic acid and

vitamin B12 would have been expected to reduce the efficacy of the pemetrexed. Unexpectedly, it does not. By using Dr. Niyikiza's invention, Lilly was able to reduce the toxicity of pemetrexed while maintaining its efficacy. And so for all of these reasons, Dr. Niyikiza's invention would not have been obvious in June of 1999.

I now want to turn to the defendant's enablement, written description, and best mode arguments. All these relate in some way to the phrase "effective amount of pemetrexed," which appears in two of the eight claims that Lilly is asserting.

Let's talk about enablement first. What you will hear from the defendants is that the '209 patent doesn't disclose what particular dosages of pemetrexed would be effective in Dr. Niyikiza's regimen and that, therefore, undue experimentation would be required to use Dr. Niyikiza's invention.

The evidence from the defendants on this defense will be fundamentally inconsistent with what you hear on their obviousness defense. They said ours is inconsistent. I'll tell you why there's is and I'll tell you why ours isn't.

For obviousness, the defendants will assert that clear and convincing evidence shows that it was obvious from the prior art how to use a regimen of folic acid, vitamin B12, and an effective amount of pemetrexed. But when it comes to

enablement, a different expert will come in and testify that with both the patent -- so both knowing the inventor's idea to do it and the prior art, the person of ordinary skill would have no idea how to use an effective amount of pemetrexed with folic acid and vitamin B12.

Ask yourself, Your Honor, they have the burden on both of these. How can there be clear and convincing evidence of either defense when they are each contradicted by one of the defendant's own experts? The reason it's not inconsistent for us, Your Honor, is before Dr. Niyikiza's invention, the person of ordinary skill wouldn't have been motivated to do this. They wouldn't have wanted to, because they would think it would reduce the drug's efficacy.

Once you know Dr. Niyikiza's idea and he tells you to go do it, it's not going to take undo experimentation to go do it. There's no inconsistency there, and so what the evidence will show is that the defendants are wrong on both defenses, and I have already talked about obviousness.

As to enablement, what the evidence will show is that the person of ordinary skill could have used an effective amount of pemetrexed in Dr. Niyikiza's invention without engaging what the law calls "undue experimentation." Mr. Wiesen put up Column 8 of the patent which gives a dosing regimen for an antifolate.

The key point I'll leave with you, Your Honor, is

there's not going to be any evidence that this regimen wouldn't be effective if you used it with pemetrexed. He said it's 100 times less pemetrexed. It's given a lot more often than 500 every three weeks, and Lilly had trials using low amounts of pemetrexed much closer together. And if you look at the defendant's own trial brief, they say that if the skilled person used this regimen, it's unclear whether the pemetrexed would even be effective.

To prove that the skilled person couldn't practice the claims using this regimen, the defendants have the burden to prove by clear and convincing evidence that the regimen is not effective. And they're not going to be able to do that as their own brief shows.

Leaving that aside, the evidence will show that the prior art contained numerous publications disclosing effective dosing regimens for pemetrexed. The specification of the '209 patent even expressly cites one in the second paragraph. Most importantly, there were multiple publications disclosing the very dose, 500 milligrams per meter squared that was later approved by the FDA, and the literature even disclosed that this regimen was the then current dosage being used in pemetrexed clinical trials. There is no dispute that this is an effective dose when used with Dr. Niyikiza's regimen. It's exactly the same dosage that's on Alimta's label today. The person of ordinary skill would have been familiar with this

dose, would have used it, and would have been able to practice Dr. Niyikiza's invention without any difficulty, let alone undue experimentation.

What I expect you will hear from the defendants over the course of the trial is that the person of ordinary skill wouldn't have known that these previously known effective dosages of pemetrexed would be effective when used with folic acid and B12 or that the patent doesn't prove that this is the case. None of that is required, Your Honor. If the person of ordinary skill would have known of or been able with routine effort to find dosages of pemetrexed to use and those dosages, in fact, worked, then the claims are enabled, and the evidence will show that's exactly the case here.

I want to touch briefly on the written description defense, which is similar to the enablement defense. The issue for written description is whether the invention claimed in the '209 patent is described in that patent, and the evidence will show that it is. The claims require giving certain amounts of folic acid and vitamin B12 and then giving effective amounts of pemetrexed, and the specification describes doing exactly that.

What the defendants are going to say is that the '209 patent does not describe what particular effective amount of pemetrexed to use with Dr. Niyikiza's invention. But the patent doesn't claim particular effective amounts, and

so there's no requirement to describe particular effective amounts.

In fact, you will hear Dr. Niyikiza's invention is not finding some specific dosage of pemetrexed to be used in his regimen. The invention is giving certain amounts of folic acid and vitamin B12 in conjunction with any amount of pemetrexed that can provide a therapeutic benefit to a cancer patient, and the evidence will show that the patent describes this invention to the person of ordinary skill.

The last thing I want to talk about is the best mode defense. The question here is whether Dr. Niyikiza had a subjective preference for using particular dosages of pemetrexed in his invention, and if he did, did he conceal those dosages when he filed his patent?

The evidence will show that Dr. Niyikiza did not have a preference for any particular dosing regimen for pemetrexed when the '209 patent was filed. Rather, he believed that his claimed methods of vitamin pretreatment could be used with any amount of pemetrexed that was effective, and you're not going to hear any evidence to the contrary.

The evidence that the defendants are going to put forward is just going to serve to show that Dr. Niyikiza was aware that Lilly was using dosages of 500 and 600 milligrams per meter squared in its clinical trials. Of course he was

aware of it, but that doesn't mean that he personally, subjectively had a preference for using these dosages in his invention.

You can only put -- you have got to put some dose in the clinical trial, and so you put a dose in the clinical trial and he knew what it was. It doesn't mean he subjectively believed that that was the best way to practice his invention. He thought you could practice his invention with any dose that was effective.

And, in fact, Your Honor, the only evidence is going to be that Dr. Niyikiza had no preference for any particular dosage. And in any event, Your Honor, there's no concealment here of the 500 and 600-milligram dosages. In fact, it's exactly the opposite.

The second paragraph of the '209 patent cites a prior art article disclosing precisely these dosages. In fact, it discloses the 600 dose on the very page that the specification cites and the 500 and 600 dose on the immediately preceding page. Hardly an act of concealment.

Let me sum up, Your Honor. As you have seen this morning, the defendants are asserting almost every invalidity defense in the patent law. It's going to be a little bit like a law school exam here for a while. They bear the burden of proof by clear and convincing evidence on all of them. The evidence will show that they cannot establish any of these

defenses, that Lilly's claims are valid, and that judgment should be entered in Lilly's favor. Thank you, Your Honor.

THE COURT: Thank you, Counsel. Okay. It's 11:00 o'clock. Do you want to take a short break and start with the first witness, or do you want to go to lunch now? What's your preference, lawyers?

MR. PERLMAN: My preference would be to take a short break and then keep going. I don't know where Mr. Wiesen is.

THE COURT: Okay.

MR. WIESEN: We're happy to put on the first witness after a short break.

THE COURT: Let's take 15 minutes, and then we'll start with the first witness.

THE COURTROOM DEPUTY: All rise.

(Recess at 11:01, until 11:25.)

THE COURT: We are back on the record. And, Counsel, you may call your first witness.

MS. RAPALINO: Thank you, Your Honor. My name is Emily Rapalino.

THE COURT: I need you to talk in the mic.

MS. RAPALINO: My name is Emily Rapalino. I'm with Goodwin Procter representing the defendants. Defendants call as our first witness Dr. Mark Ratain.

THE COURT: Okay, Dr. Ratain, if you would come right up here. We know it's tight.

Doctor, if you would remain standing and raise your right hand.

(The witness is sworn.)

THE COURT: You may have a seat.

MARK RATAIN, DEFENDANT'S WITNESS, SWORN

DIRECT EXAMINATION

BY MS. RAPALINO:

Q. Good morning, Dr. Ratain.

A. Good morning.

MS. RAPALINO: Your Honor, before I begin with the direct examination of Dr. Ratain, I just had a ministerial question for the Court about offering exhibits into evidence.

Per the parties' stipulation that the Court entered in this case, we did exchange exhibits in advance; and I believe that the parties have worked out any objections to the exhibits that Dr. Ratain intends to discuss today. And I guess the question is just for efficiency's sake, would you prefer that we offer those exhibits into evidence at the beginning of the testimony, all in a group at the end of the testimony, or as they come up?

THE COURT: And what did you want to say, Counsel?

MR. PERLMAN: My only issue, Your Honor, is if he testifies about the documents, we have no objections to their admission into evidence. I don't want to just admit the binder and then -- if he doesn't get to all the documents.

MS. RAPALINO: My proposal would be that we just wait until the conclusion of the direct examination of Dr. Ratain, and then we can offer the exhibits that he's discussed as a list into evidence if that works.

THE COURT: Okay. Fair enough. All right. And you may examine your witness.

MS. RAPALINO: Thank you, Your Honor.

BY MS. RAPALINO:

Q. Dr. Ratain, could you please state your full name -- state and spell your full name for the record?

A. Mark Jeffrey Ratain, M-a-r-k, J-e-f-f-r-e-y, R-a-t-a-i-n.

Q. Thank you. Where do you live, Dr. Ratain?

A. I live in Chicago.

Q. Are you employed?

A. Yes. I'm employed by the University of Chicago.

Q. What positions do you hold at the University of Chicago?

A. I hold a number of positions. I'm the Leon O. Jacobson Professor of Medicine. I'm also the director of the University Center For Personalized Therapeutics, and I'm the associate director for clinical sciences in the university's Comprehensive Cancer Center.

Q. Do you have any other hospital leadership positions?

A. Yes. The University of Chicago's hospital is called University of Chicago Medicine. I also have the appointment as chief hospital pharmacologist.

Q. How long have you held positions at the University of Chicago?
A. I've been on the faculty since 1986.
Q. And how long have you been a professor at the University of Chicago?
A. I've been a professor since 1995.
Q. Now, as a professor at the University of Chicago, what are your responsibilities, generally?
A. Well, I have multiple responsibilities. I'm a practicing physician, so I take care of patients. I have an active research program related to anti-cancer drugs and to variability in the effects of anti-cancer drugs. I teach primarily informal teaching of young scientists and young physicians, and I have the administrative positions I mentioned.
Q. I would like to ask you to turn in your binder that we've placed in front of you to Trial Exhibit 1507.

MS. RAPALINO: And, Your Honor, at the break, we took the liberty of providing the Court with copies of the binders, as well.

BY MS. RAPALINO:
Q. So, Dr. Ratain, if you would turn to Exhibit 1507 in your binder.

THE WITNESS: Sorry, Your Honor. I keep hitting the microphone.

THE COURT: It's very sensitive. So it makes lots of noise.

BY MS. RAPALINO:

Q. Is this a copy of your CV, Dr. Ratain?

A. Yes, it is.

Q. And did you prepare this document?

A. I did.

Q. Does it accurately reflect your education and experience?

A. Yes, with the exception of additional publications subsequent to the preparation of the document on July 25th, 2013.

Q. Okay, but with the exception of those additional publications, this is an accurate reflection of your education and experience?

A. Yes.

Q. Okay. I want to take a step back and looking at your CV, I want to just talk a little bit about your education. Where did you go to college?

A. I went to Harvard University in Cambridge, Massachusetts.

Q. When did you graduate?

A. I graduated in 1976.

Q. Did you go to medical school after that?

A. Yes. I went directly to medical school, and I graduated from Yale University School of Medicine in 1980.

Q. Did you do any postgraduate training after medical school?

A. Yes, I did six years of formal postgraduate training, three years in internal medicine at Johns Hopkins Hospital in Baltimore, and a three-year fellowship in hematology-oncology at the University of Chicago Hospitals.

Q. What did you do after you completed your fellowship at the University of Chicago?

A. As I mentioned, I joined the faculty in 1986 directly after completing my training.

Q. And at the time you joined the faculty at the University of Chicago, what were your responsibilities at that time?

A. Well, my responsibilities were somewhat similar to what they are today, although I didn't have any significant administrative responsibilities at that time, and I probably saw a bit more patients than I do today.

Q. Did you do any research at the time you joined the faculty or at the beginning of the 1990s?

A. Yes. I've had an active research program since 1986, including both laboratory research program and a clinical research program involved in the design, conduct, and analysis of clinical trials; and my primary interests since 1986 has been on understanding variability between patients in response to drugs, especially in regard to variability and toxicity of anti-cancer drugs.

Q. Can you explain just briefly what you mean by variability and toxicity to cancer drugs?

A. Well, when we treat patients with cancer, we follow a standard recipe that's prescribed either based on clinical trials or based on the FDA label. And as we've heard from the tutorial this morning, patients develop side effects from chemotherapy, but not everybody has the same degree of side effects. And some patients have a lot more side effects than others.

And so understanding that puzzle, that mystery, understanding exactly why some patients have more side effects than others, and then developing approaches to diagnose and treat that variability, that's been a fundamental part of my research program really since day one, since I first started my training in 1983.

Q. Have you ever done any research related to antifolates?

A. Yes, I have.

Q. Can you just briefly describe that research?

A. Well, I did two Phase 1 trials with a Zeneca drug, ZD9331, and I also participated in a Phase 1 trial of a second Zeneca drug, one that was subsequently approved called raltitrexed.

Q. At the time that you were doing that research, were you following the literature related to antifolates?

A. Yes. I was actively involved in antifolate research. I would go to meetings. I would make presentations in sessions and meetings. In fact, I even remember going to a meeting focused entirely on antifolates in Oxford.

Q. Were you active in any professional oncology organizations over the course of your career?
A. Yes. I've been intermittently very active in the American Society for Clinical Oncology. I say "intermittent" because I'm a former officer of the organization and served as secretary/treasurer from 1994 to 1997. And since then I've had, of course, much less of a role but have still been active in many of their committees.
Q. Can you explain a little bit more about what the American Society of Clinical Oncology is?
A. Yes. The American Society of Clinical Oncology -- which I'll refer to as "ASCO" because the term will come up again -- is the premier international society involving physicians who take care of patients with cancer.
Q. What kind of activities does ASCO engage in?
A. ASCO has a multitude of activities. Probably its most prominent activity is its annual meeting, which these days consists of about 30,000 people congregating in Chicago every June. Back in the '90s, it was probably only about 20,000, and we went to much more desirable places like Dallas and Orlando.
Q. Okay. Have you ever had any involvement with the National Cancer Institute?
A. Yes. I've been quite closely interactive with the National Cancer Institute since I joined the faculty. I've

been the principal investigator of initially a contract with the National Cancer Institute and subsequently a grant with the Cancer Institute for Phase 1 clinical trials in collaboration with the National Cancer Institute since 1989.

Q. Have you had any leadership positions within the National Cancer Institute?

A. Yes. In 2005, the National Cancer Institute decided to create an investigational drug steering committee and -- in order to provide input to the National Cancer Institute regarding the best way to design and conduct trials of new anti-cancer agents, and I was elected one of the first two co-chairs of that committee.

Q. Have you been active in any professional organizations outside of the oncology specialty?

A. Yes. I've also been very active in an organization called "ASCPT," which stands for the American Society for Clinical Pharmacology and Therapeutics, which is the premier international organization that includes academic investigators, government investigators such as the FDA, and industry investigators, all interested in the development of drugs and the administration of drugs to patients.

Q. And are there members of that society who are not oncologists?

A. Yes. Very few members of that organization are oncologists, which is one of the reasons that it's been such

an important organization for me, is to interact freely with investigators interested in drugs from other therapeutic areas.

Q. Have you published in your field?

A. Yes. I've published just over 400 papers.

Q. Can you describe generally some of the subject matter of your papers without, obviously, giving us detail about 400 of them?

A. Yes. Well, thank you. My papers fall into a variety of areas. Some of them relate to early clinical trials of investigational anti-cancer drugs, such as the kind of studies we're going to be talking about today, both Phase 1 trials and Phase 2 trials. Many of my papers relate to an area of research that I would -- I have called pharmacodynamics, which is very similar to the analysis that Dr. Niyikiza performed, where one tries to understand variability in the toxicity of a drug and conduct multivariate analyses to sort that out. And more recently my work has, in a large extent, focused on pharmacogenomics, in now that we understand that a lot of this variability we see from patient to patient is due to one's genetics.

Q. You may have explained this as part of your answer, but just for some clarity, can you explain what the word "pharmacodynamics" means?

A. Thank you. That's a great question.

There are two words that we're going to talk about probably during the course of this trial that sort of sound the same but have very different meanings. One is "pharmacokinetics," and one is "pharmacodynamics." Pharmacodynamics is what the drug does to the body, which is in contrast to pharmacokinetics, what the body does to the drug.

Q. Okay. Thank you.

Are any of your publications related to antifolates?

A. Yes, they are.

Q. And then do you have any publications that relate generally to toxicity of anti-cancer agents?

A. I have many publications that relate to the toxicity of anti-cancer agents. That's been a focus of my research in my entire career.

Q. Have you ever had a major editorial role in any journals during the course of your career?

A. Well, yes. I'm currently coeditor in chief of a journal called *Pharmacokinetics and Genomics*, which relates to this area of research that I just was discussing, the genetic variability in drugs, and I previously served as associate editor for the *Journal of Clinical Oncology*, which is the ASCO journal.

Q. Are you an inventor on any patents?

A. Yes. I have four issued U.S. patents and two issued

foreign patents.
Q. And do any of those patents relate to any issues that are of relevance to this case?
A. Yes. The patents largely relate to the work I did with an anti-cancer drug called irinotecan, which was approved by the FDA in 1996, and the problem with irinotecan was very similar to the problem with pemetrexed, which is that there was a lot of variability in the toxicity. Some patients had really horrible, severe toxicity, and we did an analysis, a multivariate analysis, and we worked out an understanding of what the variability in toxicity was due to, which then led to patent filings.
Q. Now, we're going to talk about the term "multivariate analysis" in much more detail later, but just in a couple of sentences can you just give a brief explanation of what a multivariate analysis is?
A. Well, a multivariate analysis is when you have some observation in which you have variability and you're trying to understand things that are related to that variability. And you have -- instead of just having one concept, such as you want to correlate height and weight, in this scenario you would have multiple different variables, some of which you think might be related, some of which you think probably aren't related, and some which, you know, are closely related to each other. And you throw all this data into a computer,

and you start to analyze it.

Q. Okay. We'll come back to talk about that a little bit later.

Getting back to your background, have you ever won any awards in connection with your work?

A. Yes. I've won a number of awards. I'm most proud of the awards I received from societies; professional organizations have honored me. I mentioned ASCPT. They gave me a major award a few years ago, the Rawls-Palmer Award. I also received an award from the American Association of Pharmaceutical Scientists, an award from the American College of Clinical Pharmacology, and I've received awards from other institutions, including MD Anderson Cancer Center in Houston, the University of North Carolina, and the National Cancer Institute.

Q. And generally speaking, what were those awards in recognition of?

A. These awards have been in recognition of my work regarding anti-cancer drugs and the pharmacology, the pharmacokinetics, and pharmacodynamics of anti-cancer drugs.

THE COURT: What do you get? Do you get money or trophies or --

THE WITNESS: Occasionally I get a little money. The Texans gave me money. Usually you get a plaque.

THE COURT: Okay.

MS. RAPALINO: Okay. Your Honor, I've finished the -- Dr. Ratain's qualifications section of the examination, and I'm about to move into a little bit more substance, and I just wonder in terms of taking a break, whether it makes sense to keep going for a little bit.

THE COURT: Let's keep going for a little bit.

MS. RAPALINO: Okay. No problem.

BY MS. RAPALINO:

Q. Now, Dr. Ratain, you've been engaged as an expert in this case; is that right?

A. Yes.

Q. What patent were you asked to testify about?

A. I was asked to testify about the '209 patent that we heard about earlier.

Q. Did you participate in preparing slides to assist you in testifying today?

A. Yes, I did.

MS. RAPALINO: Okay. Could we pull up Dr. Ratain's first slide?

BY MS. RAPALINO:

Q. What specific issues were you asked to consider with respect to the '209 patent?

A. Well, I considered two basic issues: One on obviousness and one on obviousness-type double patenting. I considered the obviousness of the '209 patent claims as of June 1999 in

view of the prior art, and I considered the issue of obviousness-type double patenting of the '209 patent claims over Claim 20 of the '974 patent.

Q. And were you asked to consider the prior art as of a particular date?

A. Yes.

Q. What date was that?

A. That was June 1999.

Q. What type of prior art did you review in conducting your analysis?

A. Well, I looked at scientific publications, scientific and medical publications, full publications, full articles, what I will refer to as abstracts, which are not the full article. I also looked at patents that had been published or issued.

Q. How did you obtain the literature that you just described?

A. Well, most of this I obtained through my usual due-diligence process I use in my everyday research, but some was provided to me by counsel.

Q. Were you previously familiar with the literature that you reviewed?

A. Yes.

Q. Did you look at any documents or data that were generated after June 30th of 1999?

A. Yes, I did.

Q. Can you explain a little bit more about that?

A. Well, I was also asked to consider the secondary considerations, and so there were publications that were relevant to those opinions that were not prior art.

Q. And after forming your opinions in this case, did you review any other documents besides publicly available literature?

A. Yes. I was able to review a number of documents related to correspondence between Lilly and the FDA.

Q. What conclusions did you reach concerning the obviousness of the asserted claims?

A. Well, the summary of my opinions is shown on this slide, and they are that the claims of the '209 patent would have been obvious to a person of ordinary skill in the art as of June 1999 in view of the prior art. More specifically, it would have been obvious to add vitamin B12 pretreatment to a regimen of pemetrexed with folic acid pretreatment at the claimed doses and schedules in view of the prior art.

Q. And what conclusions did you reach concerning obviousness-type double patenting in this case?

A. My opinions regarding obviousness-type double patenting are shown on this slide. A person of ordinary skill in the art as of June 1999 would have considered the asserted claims of the '209 patent to be obvious variance of Claim 20 of the '974 patent. More specifically, the asserted claims of the '209 patent covering regimens of pemetrexed with vitamin

B12 and folic acid pretreatment are obvious variance of Claim 20 of the '974 patent, which covers regimens of an antifolate with folic acid pretreatment in view of the prior art.

Q. Okay. We're going to come back and talk about each of those opinions in much more detail, but before we do that, I want to turn to talking about some of the background science that's relevant here. Now, we've been talking about the '209 patent. Very generally, what is the '209 patent directed to?

A. Well, the '209 patent is generally directed to a method of use of pemetrexed, the antifolate we've been talking about this morning, in combination with vitamins.

Q. And what specific vitamins are claimed in the '209 patent?

A. This -- the specific claimed vitamins are folic acid and vitamin B12.

Q. What classes of disease is pemetrexed used to treat?

A. Pemetrexed is used to treat two types of cancer, or it's indicated to treat two types of cancer.

Q. Let's start with cancer, then. Can you explain generally what cancer is?

A. Well, cancer isn't a disease. Cancer is a process, a group of diseases. It's really now viewed as a genetic disease in the sense that our cells within the body develop

mutations over time, and these mutations can cause a cell to, for lack of a better term, to misbehave and not act like a normal cell and therefore grow without restraint and metastasize.

Q. How is cancer treated?

A. Well, historically, the most effective treatment for cancer from the standpoint of curing the disease has been surgery. More recently, we've developed other tools: Radiation therapy, of course, which can cure some cancers; and then drug therapies, with chemotherapy being the first example of drug therapies, which unfortunately is not that effective from the standpoint of curing cancer.

Q. What is chemotherapy?

A. Well, when I'm talking to my patients who aren't that familiar with chemotherapy, I explain to them that chemotherapy is essentially poison, and really that's how it all got started. And so chemotherapy damages the tumor and, unfortunately, also has the complication of damaging the normal, healthy cells. And the purpose of the chemotherapy is to prevent these uncontrolled tumor cells from continuing to grow and metastasize.

Q. And how does chemotherapy target cancer cells?

A. Well, there are a number of different targets. Classically, the most common targets of chemotherapy have been the DNA, the underlying genetic code for the entire cell, and

drugs have been developed that block the production of the building blocks of DNA, such as antifolate drugs, but there are other drugs that actually bind directly to the DNA or prevent the DNA from dividing.

Q. And how does targeting the DNA treat the cancer?

A. Well, if the cell can't make DNA, it will die, and it certainly won't be able to replicate.

Q. So we've been talking a little bit about DNA. Can you give just sort of an overview of what DNA is?

A. Well, as I mentioned, DNA is the underlying genetic code, and its primary purpose is to direct traffic and direct the entire growth of the cell. And it does so by providing this code that results in the production of what we call messenger RNA. There are other kinds of RNA, as well, but RNA conveys a message that allows the cell to learn how to make proteins.

Q. And so what happens when chemotherapy targets that DNA?

A. Well, chemotherapy targets the DNA; then the DNA cannot make the message and the DNA cannot replicate.

Q. Does chemotherapy affect healthy cells?

A. Yes. Chemotherapy, unfortunately, affects healthy cells, particularly those that are -- have ongoing growth and division.

Q. And what kind of healthy cells typically have ongoing rapid growth and division that are particularly susceptible to chemotherapy?

A. Well, I have a slide that explains this, so there's -- I want to divide this into three areas of rapidly dividing cells. So, we have bone marrow cells, digestive tract cells and hair follicle cells as three examples of types of rapidly dividing cells.

Q. What happens when chemotherapy targets, for example, the bone marrow cells?

A. Well, the side effect -- the medical term for the side effect is "myelosuppression," and myelosuppression can refer to depression of white cell growth, depression of red cell growth or depression of platelet growth.

Q. What happens to a patient when they have a depression in their white cell growth?

A. When they have a depression in the white cell growth, the number of white cells they make is markedly decreased. Therefore, the number of white cells in the blood goes down, and that puts a patient at risk of infection.

Q. And, similarly, what happens when a patient has a depression in red blood cells?

A. Well, that's -- what happens when there's a depression of red cells is that one becomes anemic, is the medical term, and one has a lower concentration of a red cells, with fatigue being the most common symptom.

Q. And what happens when a patient has a depression of platelets?

A. Well, a depression of platelets is called thrombocytopenia, and that results in bleeding if it's not treated and it's severe.
Q. You said the second type of cell that's rapidly dividing and susceptible to chemotherapy are the digestive tract cells. What happens when those cells are affected by chemotherapy?
A. Well, they -- the digestive tract really runs from the mouth all the way to the rear, and there can be damage anywhere along that digestive tract. If it's in the mouth, the side effect is called mucositis, reflecting mouth sores. One can also have damage to the intestine, resulting in diarrhea, nausea, vomiting. And, again, other common side effects such as loss of appetite and weight loss are often due to toxicity to the gastrointestinal tract.
Q. And what happens when chemotherapy impacts the other kind of cell you've listed here, hair follicle cells?
A. When chemotherapy affects the hair follicle, the hair falls out, and the medical term for that is "alopecia."
Q. Now, you mentioned that the '209 patent was directed to the use of pemetrexed with the two vitamins. So I want to talk about just pemetrexed for a moment, and then we'll talk about folic acid and vitamin B12. What kind of drug is pemetrexed?
A. Pemetrexed is an antifol or antifolate.
Q. And is pemetrexed marketed in the United States?

A. Yes. Pemetrexed is, as we heard, is marketed by Eli Lilly and Company under the brand name "Alimta."
Q. And you mentioned that it's approved for treating two types of cancer. What types of cancer is it approved for treatment of?
A. It's approved for the treatment of mesothelioma, and it's approved for a subset of patients with lung cancer.
Q. Have you seen any other names in the literature for pemetrexed in the 1990s?
A. Yes. It was commonly referred to as "MTA," which stood for multitargeted antifolate, and it often also went by its Lilly number, LY231514.
Q. Now, the patent claims, you said, also involve folic acid. What is folic acid?
A. Well, folic acid is a form of folate. It's the form of foliate that is contained in standard multivitamins.
Q. And how is folate used in the body?
A. Well, folate is an important cofactor and is required for the production of many metabolic reactions, particularly those that involved the building blocks of DNA and RNA.
Q. What is a folate deficiency?
A. A folate deficiency is when there's an insufficient amount of folate in the body for the body to adequately perform all of its normal folate-mediated reactions.
Q. And what are some causes of an insufficient amount of

folate?
A. Well, there are a number of causes. Just any chronic disease can lead to folic deficiency; poor diet is a very common cause, and alcoholism, unfortunately, also a cause.
Q. Let's turn to talking about the other vitamin, vitamin B12. What is vitamin B12?
A. Well, vitamin B12 is a vitamin that is naturally found in animal products, dairy products, and meat.
Q. And is vitamin B12 one compound?
A. Well, from a physician's standpoint, it's really a whole host of compounds, but I understand in this case the term "vitamin 12" as applied to the claims has a specific meaning, cyanocobalamin.
Q. And so when you use the term "vitamin B12," are you limiting yourself to cyanocobalamin, or are there other forms?
A. I will try and -- when I use the word "vitamin B12," I'm referring to all types of vitamin B12, and when I'm referring to "cyanocobalamin," I will try to use the word "cyanocobalamin."
Q. Okay. What is a vitamin B12 deficiency?
A. A vitamin B12 deficiency is when there's insufficient amounts of vitamin B12 in the body to perform all normal B12 functions.
Q. And what are some of the causes of a vitamin B12 deficiency?

A. Well, one common cause is problems with the gastrointestinal tract. Vitamin B12 has a fairly complex process to be absorbed, and so damage to the stomach or damage to the intestines can cause a B12 deficiency. In addition, the elderly have an increased risk of B12 deficiency, and, of course, individuals who abstain from meat and dairy products are also destined to be B12 deficient and will require B12 supplementation.

Q. Now, we heard about this a little bit this morning in the tutorial, but is there any relationship between folate and vitamin B12?

A. Well, yes. They both -- if either one is deficient, one will get anemia, and also they -- both are required for a particular reaction that is involved in the synthesis of methionine. The reaction was described this morning called methionine synthase.

Q. And what happens if that reaction -- if there's a deficiency of B12 and that reaction can't proceed?

A. If there's a deficiency of B12 and that reaction can't proceed, then the homocysteine, which is the starting point for that reaction, builds up and there's increased amounts of homocysteine present in the blood.

Q. Okay. Now, you said earlier that pemetrexed is an antifolate. Can you describe generally what antifolates are?

A. Well, antifolates are a class of anti-cancer drugs that

have a similar chemical structure to folic acid and block one of the enzymes, the folate pathway that we heard about earlier, and therefore interfere with the synthesis of DNA and/or RNA.

Q. Can you explain a little bit about what enzymes are?

A. Yes. An enzyme is a protein that has -- that is capable of carrying out a specific biochemical reaction, and so enzymes generally have a particular type of substrate. Enzymes can have more than one substrate, and they will bind to that substrate and -- kind of like a lock and key, and then carry out this chemical reaction, forming one or more products.

Q. And you used the term "substrate." What is a substrate?

A. Substrate is the starting point for the reaction.

Q. Okay. And what are some of the -- what are some of the enzymes that antifolates target?

A. Well, there's four that have been identified that are important from the standpoint of a number of different anti-cancer drugs. We heard the abbreviations this morning: DHFR, dihydrofolate reductace; TS, thymidylate synthase, GARFT and AICARFT.

Q. Thanks. Now, looking back historically, what were the first antifolates that were developed?

A. Well, the first antifolate that was tested in patients was aminopterin.

Q. And have other antifolates been developed since?
A. Yes, methotrexate has been in clinical use for probably about 50 years now.
Q. What has methotrexate been used for?
A. Methotrexate is used for a variety of different cancers, and it's also used for the treatment of rheumatoid arthritis.
Q. Are there other examples of antifolates that have been in development over the years?
A. There are many antifolates that have been in clinical trials. There -- we're obviously talking about pemetrexed, of course, which is another antifolate that is approved by the FDA. There are other Lilly compounds that I will be discussing, lometrexol, and a compound called the '887 compound. I also mentioned my work with raltitrexed and ZD9331, and I will add that raltitrexed is approved in Canada and in some European countries.
Q. What was the state of antifolate drug development in the 1990s?
A. This was a very active area, as I mentioned. There were whole sessions of meetings and whole meetings just on antifolates.
Q. And were any antifolates in clinical trials as of the 1990s?
A. Yes. There are a number of antifolates in clinical trials in the '90s, and all three Lilly compounds that I mentioned

and the two I worked on were under development in the 1990s, as examples.

Q. Okay. You talked earlier about the effect of antifolates on DNA and cells. How do antifolates get into the cells to exert their effect?

A. Well, there's at least two transporters. A transporter is a protein that moves a molecule across a cell membrane, the boundary between the inside and outside of the cell. And the two that are -- have been associated and mediate the transfer of antifolates are the RFC, or reduced folate carrier, and the FBP, or folate binding protein.

Q. Okay. Let's talk for a moment about the process of drug development. Generally, can you describe what kind of testing has to be done before a drug can be put into a patient?

A. Well, there's really a large number of steps that are required before the FDA will permit the initiation of clinical trials, and this is -- we call this the preclinical process, the steps that lead up to what's called an IND, Investigational New Drug Application. So there's a large number of steps. There's -- first there's the basic discovery of the molecule and the demonstration that the molecule does something, and these kinds of studies are done just in test tubes or against cancer cells growing in a plate.

Q. What comes after that?

A. After that, the next step is, once you know -- once you

know you have a drug that works against a cancer cell growing on a plate, the next question is, well, if I give the cancer drug to a mammal, can I get enough drug into the tumor to get anti-cancer effect? And so there are a number of animal models that have been developed for the testing of anti-cancer drugs, and one particular kind of model is one where human cancers are transplanted into mice.

Q. Is there a name for that kind of model?

A. Yes. That's called a xenograft model.

Q. And how common was the use of a xenograft model in the 1990s?

A. It was one common type of model. It required a special kind of mouse that did not reject the human cancer. But, there were many, many different models.

Q. Now, are there other types of preclinical tests that would be done before a drug would make it into a patient?

A. Well, it would be pretty routine, for example, to do pharmacokinetics of the drug in mice, rats, dogs, sometimes rabbits. And I mentioned that pharmacokinetics is what the body does to the drug, because one of the things you would like to know if you're going to give a drug eventually to patients, you would like to have an idea of how much drug it takes in the blood to work in the patient. So by doing these studies in animals, you can get that understanding.

Q. And are there any other types of preclinical testing that

are done before a drug moves into clinical trials?
A. Yes. Usually the last type of scientific experiment is what's referred to as toxicology studies, where one wants to really understand the side effect profile of the drug, particularly the side effect profile of the drug at potentially lethal doses and the dosage that results in fatality because, again, that greatly influences the design of the human clinical trials.
Q. Now, assuming that a drug shows promise in these preclinical tests, what's the next stage?
A. Well, as I mentioned, the next step would be, if a company wants to proceed to clinical trials, is they package up all these experiments into a large document reporting the results of all these studies, and in addition, they have to write what's called a protocol for the first Phase 1 trial. A protocol is a written document that is reviewed by an ethics committee -- and we call them in this country institutional review boards -- that makes sure that the experiment is reasonable and that the consent form is reasonable. And then that protocol plus all these preclinical data goes to the FDA, and the FDA then makes an assessment as to whether it's reasonable to begin clinical trials.
Q. And if the FDA decides it's reasonable to begin clinical trials, what's the first kind of clinical trial that's conducted?

A. This first kind of clinical trial is what we call a Phase 1 trial; and for cancer drugs, it's performed in cancer patients, cancer patients that -- for whom there is no standard therapy, for whom that are resistant to all approved drugs.

Q. And how are Phase 1 trials for anti-cancer drugs generally designed?

A. Well, it's -- it's a process where the first patients, unfortunately, often get treated at doses that the investigators might believe are too low a dose, because the FDA makes us err on the side of caution. So you start at a dose that is one-tenth of the dose that you think is the effective dose, and then you increase the dose in groups of patients until you get to what's called the maximally-tolerated dose.

And so the purpose of this Phase 1 trial generally is to define the maximum tolerated does.

Q. Is it a goal of a Phase 1 study to evaluate the efficacy of a drug?

A. It's a goal from the patient's perspective to have efficacy. It's a goal of the physician who is actually treating the patient for the patient to have efficacy, but the study is not a scientific experiment that can measure efficacy.

Q. So can the results of Phase 1 trials be compared to

reliably ascertain the relative efficacy of the regimens of two different Phase 1 trials?

A. No.

Q. Why not?

A. Well, as I mentioned, Phase 1 trials have a variety of different doses, and so patients are getting all different doses.

In addition, patients have -- basically have tumors that are resistant to prior therapy; and so they may have a disease that will never respond to anything, for example, in a Phase 1 trial, or they might have a disease that has responded in the past, and the patient's physician does not want to re-treat them with the same drug again, and that's a different kind of patient.

In addition, over the years, we have more and more drugs approved; and so that patients now that go on Phase 1 trials have had many more drugs than patients that had went on Phase 1 trials when I first started doing Phase 1 trials in the 1980s.

Q. So are all the patients receiving a particular drug in various Phase 1 trials? Do they all have the same kind of cancer?

A. No. They all have different cancers.

Q. Now, I know you said that Phase 1 studies are not designed to evaluate efficacy of a drug. Is it possible to glean any

information about efficacy from a Phase 1 trial?
A. Well, yes, particularly when one looks at a portfolio of Phase 1 trials; and it's well established that every drug that we have on the market today showed some efficacy in at least one Phase 1 trial. That's not to say that every Phase 1 trial had at least one patient with efficacy, and it certainly doesn't mean that every patient in a Phase 1 trial showed efficacy. But, as I always tell my patients, if this drug is going to be approved by the FDA, somebody is going to respond to it in a Phase 1 trial.
Q. Now, what happens after Phase 1 trials if a drug continues in its development?
A. Well, assuming that there is agreement that the Phase 1 schedule, in other words, the frequency of administration, every three weeks or weekly or whatever that initial trial was, is the right one, then one would proceed to a Phase 2 trial designed to measure the efficacy of a drug in a particular disease with the goal of trying to make an assessment as to whether it's worth investing for a large Phase 3 clinical trial.
Q. And if a company decides that's it's worth the investment for a large Phase 3 clinical trial, can you describe what happens in a Phase 3 clinical trial?
A. Well, a Phase 3 clinical trial must meet very strict regulatory standards; and so there's extensive discussions,

both within a company with investigators, and potentially with the FDA -- and certainly today that is almost always done; but generally, even in the '90s, companies would meet with the FDA at the end of Phase 2 to plan Phase 3 trials. These would be large randomized trials where half the patients get a control group of some standard therapy, and the other half of the patients get the therapy that the company is trying to get approved by the FDA.

Q. And can you describe generally the design of a Phase 3 trial?

A. Well, Phase 3 trials are what we call randomized trials. Sometimes they're what we call double-blind trials where nobody knows what the patient is getting, whether they're getting the standard or the experimental, although in oncology, and for example, with pemetrexed, that was not a double-blind trial. But, the Phase 3 trial, pemetrexed in mesothelioma, for example, compared patients with cisplatin, a standard therapy, versus a combination of cisplatin with pemetrexed.

Q. Okay. I would like to turn from talking about some of the background science to focusing more on the patent-in-suit in this case.

MS. RAPALINO: And again, before I do that, Your Honor, I just want to check and see whether this might be an appropriate time for a break. I'm about to turn to something

new.

THE COURT: If you would like to break now, we can break now.

MS. RAPALINO: Okay. I think maybe we'll take a lunch break?

THE COURT: Okay. We'll take one hour. We will resume at 1:00 p.m. Enjoy your lunch, everyone.

THE COURTROOM DEPUTY: All rise.

(Recess at 12:07, until 1:19 p.m.)

A F T E R N O O N S E S S I O N

THE COURT: Good afternoon. We are back on the record. And, witness, you are still under oath. You were previously sworn this morning, and you may continue with your direct examination.

MS. RAPALINO: Thank you, Your Honor.

BY MS. RAPALINO:

Q. Good afternoon, Dr. Ratain.

A. Good afternoon.

Q. I would like to turn to the '209 patent at issue in this case now. Can you just remind the Court what generally the '209 patent is directed to?

A. The '209 patent is directed to methods of using pemetrexed with folic acid and vitamin B12 pretreatment.

Q. And which claims are currently being asserted in this case?

A. There are currently eight asserted claims, 9, 10, 12, 14, 15, 18, 19, and 21.

Q. Are those the only claims that you analyzed in this case?

A. No. I analyzed all claims of the '209 patent.

Q. Okay. Let's start with the first two of the asserted claims, Claims 9 and 10. If you could turn in your binder to Trial Exhibit 1, that's the '209 patent.

And if we take a look at Claims 9 and 10 in Trial Exhibit 1, they're at Column 11. Are Claims 9 and 10

dependent or independent claims?
A. They are dependent.
Q. What claim do they ultimately depend from?
A. From Claim 1.
Q. I would like to start by looking at Claim 1. And could you tell us what Claim 1 covers?
A. Claim 1 covers a method for administering pemetrexed disodium to a patient in need thereof, comprising administering an effective amount of folic acid and an effective amount of a methylmalonic acid-lowering agent, followed by administering an effective amount of pemetrexed disodium wherein, and then there's a list of possible methylmalonic acid-lowering agents.
Q. What's the relevant methylmalonic acid-lowering agent for purposes of this case?
A. Vitamin B12.
Q. Did you apply any claim constructions in rendering your opinions regarding Claim 1?
A. Yes, I did.
Q. Where did you obtain those constructions?
A. I obtained them from counsel, and I understand that these are claim construction that has been based on an opinion of the Court.
Q. Okay. And is -- does this slide reflect the claim constructions that you applied in this case?

A. Yes.
Q. Okay. I want to just take a moment and focus on one of those constructions. It's the construction of the term "an effective amount of pemetrexed disodium." And the construction you've listed on the slide is "an amount of pemetrexed disodium that is capable of providing a therapeutic benefit to the patient in need thereof." What is a therapeutic benefit?
A. Well, a therapeutic benefit in the context of a cancer patient is a benefit in quality of life, quantity of life, or potentially in an end point such as a tumor size, where the tumor size may shrink, that would be considered a therapeutic benefit or the patient may have an improvement in symptoms or they may live longer.
Q. Okay. Let's turn to your opinions in this case. You indicated earlier that you had concluded that the claims of the '209 patent would have been obvious to a person of ordinary skill in the art. Have you applied a particular framework in determining whether the asserted claims are obvious?
A. Yes, I have.
Q. And what was the framework that you applied?
A. Well, the first thing I considered was the qualifications of a person of ordinary skill in the art, which I'll refer to as a POSA, just for efficiency, the scope of the prior art,

the differences between the prior art in the claims; and then I determined whether the claims were or were not obvious in view of the prior art.

In addition, I considered whether the POSA was motivated or not motivated to practice the methods of use in the '209 claims and whether or not the POSA would have had a reasonable expectation of success.

Q. Now, you used the phrase "reasonable expectation of success." What do you mean when you say "a reasonable expectation of success"?

A. What I mean here is that the POSA would have believed that it was likely that one or more patients would be able to obtain a therapeutic benefit based on using the combination of pemetrexed, folic acid and B12 with the vitamins administered prior to the pemetrexed.

Q. A couple of times you've used the expression "person of ordinary skill in the art" or POSA, as you've abbreviated it. Have you considered what the qualifications and level of skill that the person of ordinary skill in the art would be?

A. Yes, I have.

Q. And what would you consider to be the qualifications of the person of ordinary skill in the art?

A. Well, I defined a POSA for the purpose of my opinions as an individual or a hypothetical person in June of 1999 who would have had a medical degree with additional qualifications

or experience in the field of nutritional sciences and/or oncology and practical experience in a clinical setting or academia. Such a person would have collaborated with individuals in other areas of medicine such as oncology, hematology, clinical pharmacology, nutritional sciences, including biochemistry and/or pharmacology.

Such a person would have also collaborated with individuals with expertise regarding the use of antifolates, including the use of antifolates with vitamins.

BY MS. RAPALINO:

Q. Okay. I want to explore a little bit about how you reached that opinion. What was the problem facing oncologists in the use of antifolates and chemotherapy generally?

A. Well, as I mentioned, my entire career has been focused on trying to understand the variability and toxicity of anti-cancer drugs. This was a problem for pemetrexed. There was variability and toxicity, and so a person of ordinary skill in the art was faced with the challenge of trying to understand the variability; and it was known that variability and nutrition was an important contributing factor to the toxicity of pemetrexed and antifolates in general.

Q. And so how did that information contribute to impact your definition of a person of ordinary skill in the art?

A. Well, oncologists have some familiarity with nutrition; but if one is considering trying to develop predictive tests

or trying to develop strategies involving manipulation of nutrition, an oncologist would need to interact, collaborate, and consult with an expert in nutritional sciences.

Q. Let's talk about the next part of the analytical framework that you used, which was the scope of the prior art, or the state of the prior art as of June 1999. What did you find was the state of the prior art with respect to pemetrexed as of June 1999?

A. I found that there was a lot known about pemetrexed in June of 1999.

Q. Can you be more specific?

A. Well, yes. For the sake of clarity, I've listed five bullet points on this slide; and I would like to go through each of these, but let me just summarize them right now.

First of all, pemetrexed was known to be a promising anti-cancer agent.

Second, folic acid had been used with antifolates and with pemetrexed specifically to ameliorate toxicity.

Third, poor nutrition predicts toxicity of chemotherapy, including antifolates generally and pemetrexed in particular.

Four, homocysteine was used as a marker for folate and vitamin B12 deficiency; and finally, vitamin B12 had been used with antifolates.

Q. Okay. Let's take each of those five bullet points, each

of those five categories and talk about them in a little more detail.

Let's start with the fact that pemetrexed was known to be a promising anti-cancer agent. What did the prior art literature say about pemetrexed's activity?

A. Well, there was great enthusiasm in the prior art regarding the activity of pemetrexed. It was known to be a promising anti-cancer agent. It was known to be unique among the antifolate drugs in development and that by definition, its name was MultiTargeted Antifolate. It had showed activity against a variety of tumor types, and its toxicities were fairly typical of anti-cancer agents.

Q. Were there particular references that you looked at that were available to the person of ordinary skill in the art as of June 1999?

A. Yes.

Q. Can you give me some examples?

A. So, a number of these references were contained in a single issue of *Seminars In Oncology* published in April of 1999.

Q. And what were the circumstances of the publication of that issue of *Seminars In Oncology* in April of 1999?

A. Well, these were publications based on the Proceedings of Investigators' meeting sponsored by Eli Lilly and Company held in Ixtapa, Mexico in March of 1998.

Q. What was the purpose of that meeting in Ixtapa, Mexico in March of 1998?
A. Well, I've been to investigator meetings before; and such meetings are generally designed to bring together experts in the field, especially experts working with a particular drug, to try to come to some consensus about the state-of-the-art and plans for future development.
Q. And would a person of ordinary skill in the art as of June 1999 have been aware of this April '99 supplement to *Seminars In Oncology*?
A. Yes.
Q. Okay. I would like to briefly take a look at a couple of the articles from that supplement. If you could turn in your binder to Trial Exhibit 1151, please.
Can you explain to the Court what this article is?
A. Well, this article is entitled "Overview of Phase 2 Trials of MTA, Pemetrexed, and Solid Tumors"; and the first author is Peter O'Dwyer, who is with us today.
Q. And where was this article published?
A. This article was published in *Seminars In Oncology*.
Q. And is that that same supplement that you just mentioned?
A. Yes. This was one of the articles in that supplement.
Q. And are you familiar with Dr. O'Dwyer?
A. Yes. We've known each other for a long time. We work in the same area. We've collaborated on studies together.

Q. Generally speaking, what is this article about?
A. Well, this article provides an overview of the Phase 2 trials of pemetrexed as of the date of this publication, both completed trials and ongoing studies.
Q. Okay. Let's take a look at the data that's reported in the article. If you could turn to page 101, Bates Number 789, in Trial Exhibit 1121 and take a look at Table 2. Can you explain what Table 2 shows here at the top of the page?
A. Well, Table 2 entitled "Phase 2 Activity of MTA, Pemetrexed, and Gastrointestinal Cancers," reports the results of a number of Phase 2 trials in colorectal cancer, pancreas cancer, and cancer of the esophagus.
Q. What does it generally show about the responses in those cancers from pemetrexed?
A. The study showed multiple responses, especially in colorectal cancer; and in addition, there were two responses in pancreatic cancer, including one complete response.
Q. And moving on to Table 3 at the bottom of that same page, what does Table 3 show?
A. Table 3 is focused on the studies of pemetrexed in breast cancer.
Q. And what does it report about responses in that type of cancer?
A. Table 3 reports significant activity responses of pemetrexed in breast cancer.

Q. And if you turn the page and look at Tables 4 and 5 on pages 102 and 103 respectively -- those are Bates Number 790 and 791 -- what's reported in those tables?
A. Well, Table 4 is focused on Phase 2 studies in lung cancer, and, again, it shows -- the table shows significant activity of the drug in that disease.
Q. And in Table 5?
A. And Table 5 tabulates the results of Phase 2 studies in four different cancers: Head and neck cancer, bladder cancer, kidney cancer and cervical cancer; and there were at least two responses in each of these studies.
Q. What does Dr. O'Dwyer's article conclude about the activity of pemetrexed as an anti-cancer agent?
A. Well, the concluding section entitled "Conclusion," states, "MTA, pemetrexed, has shown a broad spectrum of clinical activity in multiple tumor types, including colorectal, breast, non-small cell lung, pancreatic, head and neck, bladder, and cervical cancers.
Q. And what, if anything, does the O'Dwyer article report about pemetrexed's toxicity?
A. The conclusion states, "The toxicity profile of MTA is typical of an antifolate with myelosuppression being the most common toxicity and mucositis, rash, and fatigue occasionally being dose-limiting." In other words, these are typical toxicities not only of an antifolate but of chemotherapy in

general.
Q. Have you reviewed the entire O'Dwyer article at Trial Exhibit 1151?
A. Yes.
Q. And do the data presented from each of the clinic trials in this article support the conclusions about activity and toxicity of pemetrexed?
A. Yes.
Q. So what would the person of ordinary skill in the art understand about pemetrexed's development and its activity as of June 1999?
A. Well, a person of ordinary skill in the art would understand that pemetrexed was a very exciting drug, had an activity as defined by partial responses in many different solid tumors and that had toxicity that at least appeared to be in the acceptable range.
Q. Let's take a look at another article from this same supplement. If you could turn to Trial Exhibit 907, please, in your binder.
Can you explain what this trial exhibit is?
A. This is an article entitled "MTA summary and conclusions," and it's the wrap-up article in the same issue of *Seminars in Oncology*.
Q. And who is the author of this article?
A. Hilary Calvert.

Q. Do you know who Dr. Calvert is?
A. Yes, I do know Dr. Calvert. We have worked again in the same field for many years. Dr. Calvert is an English oncologist and clinical pharmacologist who did a lot of the early work on pemetrexed and other antifolates.
Q. What does Dr. Calvert's article say about the activity of pemetrexed in this summary article?
A. Well, there's a section in the summary article entitled *Does MTA Have Promising Activity?* I won't go through the first half of this because it basically reiterates and summarizes the work that I just described from the O'Dwyer paper, but the conclusion of this section is noteworthy. Dr. Calvert stated, "Of particular interest is the observation made in the combination Phase 1 study of MTA and cisplatin in which four to seven patients with mesothelioma have been reported as responding. If confirmed in a larger study, this is a truly exceptional result in a very refractory tumor. Overall, the breadth and consistency of the Phase 2 activity reported with MTA is remarkable and unusual in a new drug of any class at this stage of its development."
Q. So what is Dr. Calvert saying about the activity of pemetrexed?
A. Well, what Dr. Calvert is saying is that he is very impressed, and if one wanted to read this, one could take -- could translate this into this is one of the best drugs I've

ever seen.
Q. Okay. And does Dr. Calvert say anything about the targets, pemetrexed targets in the body?
A. Yes.
Q. And what does he say about that?
A. Well, he discusses this in the earlier part of the article and states that "initial testing suggested that it was, in fact, functionally a TS" -- that's thymidylate synthase inhibitor -- "but further evaluation showed that it also inhibited DHFR as well as GARFT and AICARFT." In other words, he's explicitly reminding everybody that the drug is not just a single targeted antifol, but it inhibits all desirable targets of antifolates.
Q. Now, were there other references as of June 1999 that discuss the promising activity of pemetrexed?
A. Yes.
Q. And just for the record, is this a slide that you've prepared that shows some of the additional prior art references you've reviewed in that regard?
A. Yes. I have reviewed all of these additional prior art references, and they all support the concept that pemetrexed was known to be a promising anti-cancer agent.
Q. And just for the record, can you read into the record the list of exhibits that you have reviewed in this regard?
A. Yes. These are Trial Exhibits 401, 1479, 1087, 1009 and

78.

Q. Okay.

MR. PERLMAN: Your Honor, this is the issue I was raising before. If Dr. Ratain is going to have an entry on a slide and just call out the numbers of references in support of a point and not testify about the article directly, I don't know that it's appropriate that the article be admitted. Certainly his testimony is on the stand and it's admitted, but this was the concern I perhaps inartfully tried to raise at the beginning of this. So I ask for some guidance as to Your Honor's view on this subject.

MS. RAPALINO: Dr. Ratain will likely testify about at least some portion of the articles that are listed on his slides in more detail, and just as a matter of efficiency, these are all articles that are in the record and unobjectionable and that Dr. Ratain has relied on in his expert reports to make these same points. And so just as a matter of efficiency, rather than have him go into each of the articles and describe in a redundant way that each of them make this same point, we just wanted to get them into the record this way just for a few of them. It won't be all of them.

MR. PERLMAN: Your Honor, it puts me in a difficult position on cross-examination, because now it's like a deposition where he hasn't really testified about the article

on direct. He just said the article supports this overall point, and I'm left here now to create the record that I have to cross.

THE COURT: Okay. Well, then you will need to have the doctor refer to the particular portions of these exhibits that support his testimony.

MS. RAPALINO: Okay.

THE COURT: Okay?

MS. RAPALINO: Okay.

THE COURT: We're going to look at 401?

MS. RAPALINO: Well, you know, I think the way we'll do it, is that some of these are going to come up, as I said, in any event. They're going to come up later in the examination, so to the extent --

THE COURT: Of which witness?

MS. RAPALINO: Of this witness, so to the extent they don't, I may come back and have him just point to the parts of the references that support his part of the opinion, but at least for this particular, this particular list, the majority of these will come up later in the examination.

THE COURT: Very good.

BY MS. RAPALINO:

Q. Okay. Dr. Ratain, I would like to move on to -- well, just before we move on, can you just summarize then what a person of ordinary skill in the art as of June 1999 would have

concluded about pemetrexed's activity?
A. A person of ordinary skill in the art in June of 1999 would have known that pemetrexed was a unique antifol targeting four different targets, that it had widespread activity, and to some extent remarkable and exceptional activity and that the toxicity of the drug was relatively modest, certainly moderate by oncology standards.
Q. And what would a person of ordinary skill in the art have known about the stage of pemetrexed's development as of June 1999?
A. A person of ordinary skill in the art would have also known that pemetrexed was in Phase 3 clinical trials in June of 1999.
Q. Okay. I would like to then turn to, move to the next category of information that you said was part of the state of the prior art as of June 1999, and that was that folic acid had been used with antifolates and with pemetrexed specifically to ameliorate toxicity. When was the first documented use of folic acid with an antifolate?
A. That was in 1948.
Q. And what was that first use of folic acid with antifolate in 19 -- with an antifolate in 1948?
A. That was a study by Sidney Farber, published in *The New England Journal of Medicine*.
Q. Would you turn in your binder to Trial Exhibit 1443,

please?

Is this the article that you were referring to?

A. Yes, it is.

Q. And who is Dr. Farber?

A. Well, Dr. Farber is one of the pioneers in oncology, and, in fact, the Dana-Farber Cancer Institute at Harvard Medical School is named for him.

Q. You said this was published in *The New England Journal of Medicine*. Is that a prominent publication?

A. It was and still is a very prominent medical journal.

Q. Now, what does the Farber paper from 1948 report that Dr. Farber administered?

A. Dr. Farber administered crude liver extract as well as folic acid and folic acid conjugates.

Q. And what was the purpose of administering the crude liver extract and the folic acid and its conjugates?

A. Well, Dr. Farber had observed, as noted in the paper, toxic effects included stomatitis. Stomatitis is the same as mucositis, mouth sores, with early ulceration. And then Dr. Farber went on to state, "in an attempt to prevent this complication, crude liver extract was employed as were folic acid and folic acid conjugates."

Q. And I think you may have mentioned this, but just to be clear, what was the antifolate that Dr. Farber was administering here?

A. Aminopterin.
Q. Has folic acid been administered with any other antifolates since Dr. Farber's administration of folic acid with aminopterin?
A. Yes, it has.
Q. For which antifolates has folic acid been administered?
A. It has been -- folic acid has been administered with methotrexate, with lometrexol, with the Lilly '887 compound, and it has also been administered with some nonLilly compounds.
Q. Was there literature that described the results of the use of folic acid with these other antifolates?
A. Yes.
Q. Were any of these other antifolates compounds that were being developed by Lilly?
A. Yes. Lometrexol and the '887 compound were being developed by Eli Lilly.
Q. And did Eli Lilly publish the results of the administration of folic acid with these other Lilly compounds that were antifolates?
A. Yes. They published extensively on this topic.
Q. And what would a person of ordinary skill in the art in June of 1999 take away from the fact that there were expensive publications on the administration of folic acid with antifolates?

A. A person of ordinary skill in the art would understand that the use of folic acid with antifolates was a feasible approach. They would also understand that Lilly, one of the leaders in antifolate development, was highly committed to using this strategy.

Q. Let's talk about folic acid pretreatment. In any of these instances where folic acid was given with an antifolate, was folic acid ever used as a pretreatment?

A. Yes.

Q. And were -- was the use of folic acid as a pretreatment published in a prior art?

A. Yes, it was.

Q. Let's take a look at some examples of that, if we could. If you could turn in your binder to Trial Exhibit 1036.

And could you explain to the Court what this trial exhibit is?

A. This is a paper that was published in 1996 in the journal *Investigational New Drugs*. It reports the results of a Phase 1 study of the Lilly drug lometrexol given with oral folic acid.

Q. What was the study that's reported in this article designed to test?

A. This study was designed to test if the maximally tolerated dose of lometrexol was higher in conjunction with folic acid supplementation.

Q. And can you explain what you mean by "maximally tolerated dose"?
A. Well, as I explained, Phase 1 studies are designed to ask a relatively simple question: What is the mathematically highest dose that is tolerable in a relatively small cohort of patients? And so, there had been prior studies with lometrexol, and the doses that were tolerated were quite low. And so this study was performed to see if you could administer a higher dose.
Q. And what was the design of the study in terms of the timing of folic acid administration?
A. Well, folic acid was given daily as a single 5 milligram tablet for seven days prior to and seven days following lometrexol administration. And the folic acid was provided by approved prescription services.
Q. What were the results of the study that's reported in Trial Exhibit 1036?
A. Well, this study was considered a success, and as the author stated, "In summary, the work described in this report has demonstrated the lometrexol toxicity can be modulated by folic acid supplementation in patients."
Q. And did you review the data reported in this Trial Exhibit 1036?
A. Yes, I did.
Q. Did the data support the conclusion of the authors that

folic acid could be used to modulate the toxicity of lometrexol?

A. Yes, because one could increase the maximally tolerated dose of lometrexol compared to prior study in the absence of folic acid supplementation.

Q. Was the use of folic acid pretreatment used with any other antifolates besides lometrexol?

A. Yes, it was.

Q. Which other antifolates are you aware of where there was folic acid pretreatment reported?

A. It was also used with the '887 compound.

Q. And did you review any publications reporting on the results of the use of folic acid pretreatment with the '887 compound?

A. Yes, I did.

Q. What publications have you reviewed?

A. This was described and reported in a book chapter by Mendelsohn.

Q. Okay. Could you turn in your trial exhibit binder to Trial Exhibit 400, please?

Is this the book chapter you were referring to?

A. Yes, it is.

Q. Who's the editor of the book?

A. The editor of the book is Ann L. Jackman.

Q. Who is Dr. Jackman?

A. Dr. Jackman is a scientist in the UK who -- really her entire career has been the pharmacology of antimetabolites, including antifolates. She's not an oncologist, but she's a cancer researcher.
Q. And this is Chapter 12 of the book. Who are the authors of this chapter of the book?
A. Well, the authors of the book are three individuals who were Lilly employees at the time, Mendelsohn, Worzalla, and Walling.
Q. Generally speaking, what does this chapter discuss?
A. Generally speaking, this chapter discusses two drugs, lometrexol and the successor compound, the compound I've been referring to as the '887 compound.
Q. And does the chapter describe the results of folic acid use with either of those two compounds?
A. Yes, it does.
Q. Okay. If we could turn in Trial Exhibit 400 to page 271 and focusing on Table 6 on page 271. That's Bates Number 2394. Can you explain what's reported in Table 6 in the chapter?
A. Yes. Table 6 is entitled "Effect of increasing folic acid supplementation on the therapeutic index." Let me just walk the Court through this table. So first of all, these are animal models of cancer, and there's two different models. One is called the GC3, and one is called the 3CH. And the

former is a rough model of colon cancer, and the latter is a rough model of breast cancer.

It also reports the results of two different drugs. On the -- the column all the way to the right is lometrexol, and the second to the right is the successor to lometrexol, the '887 compound. And then, for each of these drugs and for each of these tumors, four different doses of folic acid were used ranging from doses of 0.6 to 60 milligram per kilogram per day; and in addition, animals were also treated without folic acid supplementation.

Q. Can you explain in the table what therapeutic index means?

A. Yes, therapeutic index is conceptually, is physicians talk about therapeutic index all the time. It's when you're going to do something or particularly when you're going to prescribe a drug. It's the concept that you want the benefit to exceed the risk.

Q. And so what does a higher therapeutic index indicate?

A. A higher therapeutic index indicates a better drug, that the benefit relative to the risk is improved.

Q. Okay. And what are the results that are reported in this table for the use of folic acid with the '887 compound?

A. Generally speaking, the data showed; that is, the folic acid supplementation was increased from zero to higher doses, that there was an increase in the therapeutic index. In particular, you can see for one of the models, the optimal

appeared to be 15 milligram per kilogram per day. That would be the GC3 colon model and for the C3H model, the optimal folic acid dose was 6 milligram per kilogram per day.

Q. Okay. And does this same chapter describe any clinical studies using folic acid pretreatment with the '887 compound?

A. Yes, it does.

Q. And if you take a look at page 277 of the chapter, can you explain what the design was, what the administration schedule was of folic acid in the clinical studies using the '887 compound?

A. Well, the clinical study using the '887 compound used exactly the same schedule as the clinical study using the lometrexol compound, and that's stated explicitly in the highlighted sentence. The latter schedule is, therefore, identical to that used in the lometrexol study performed by Laohavinij, et al.

Q. And that study by Laohavinij, et al., what is that study?

A. That is the previous exhibit that we looked at, the Phase 1 study of lometrexol.

Q. Okay. I would like to go back for a moment to page 270 of this chapter from Chapter 12 of Exhibit 400. What does this chapter say in general regarding folic acid pretreatment?

A. Well, the chapter in general discusses the importance of folate status and makes some explicit statements. Furthermore, dietary supplementation with folic acid may

"normalize the dose response for achieving antitumor activity and reduce toxicity to normal tissues by restoring folate pools in tissues having low folate requirements without meeting the high folate demands of rapidly dividing tumor cells."

Q. What would a person of ordinary skill in the art as of June 1999 understand then from this chapter about the role of folic acid?

A. A person of ordinary skill in the art would understand that the use of folic acid with antifols, including GARFT inhibitors or related compounds, was an important concept that was under investigation by Eli Lilly.

Q. And what would they understand specifically about the role folic acid played in reducing toxicity?

A. Well, they would understand that folic acid would potentially allow one to "normalize the dose response." And that's similar to the concept I discussed earlier, the concept that one would like to understand the variability between patients by normalizing the dose response, the concept would be that you would make it so that the result of any particular dose would be predictable.

Q. Okay. And I want to look at one last reference that was listed on your slide about the use of folic acid with antifolates and in the context of pretreatment specifically. If we could look at Trial Exhibit 916, please.

Can you explain what this trial exhibit is?
A. Yes. This is the patent that I mentioned earlier, the '974 patent.
Q. And to whom is this patent assigned?
A. This patent is assigned to Eli Lilly and Company.
Q. And when did the patent issue?
A. The patent issued June 8th, 1993.
Q. Generally speaking, what is the patent directed to?
A. The patent is generally directed to the concept of administration of a folate prior to administration of an antifolate.
Q. And what's the purpose of administering the folate prior to the antifolate according to the specification of the patent?
A. Well, it's explicitly stated in the abstract of the patent that "administration of a folate binding protein binding agent in conjunction with use of an antitumor agent, which is a inhibitor of glycinamide ribonucleotide transformylase" -- that is GARFT -- "or other antifolate reduces the toxic effects of such agent and provides an enhanced therapeutic index."
Q. So what is the patent saying is the purpose of administration of the folic acid?
A. Well, the patent is saying that one can conceptually utilize folate, a folate binding protein -- a folate binding

protein binding agent; and therefore, can reduce toxicity with folate without adversely affecting therapeutic efficacy.
Q. And I think you used the term "folate binding protein binding agent." In the context of this patent, what is that talking about?
A. Yes, it's kind of convoluted. A folate binding protein binding agent is folic acid.
Q. Okay. Let's take a look at Claim 16 of the '974 patent, and what is Claim 16 -- what method does Claim 16 cover?
A. Claim 16 covers a method for reducing the toxicity of a GARFT inhibitor or other antifolate which binds to a folate binding protein. Any mammal which comprises pretreating the mammal with folic acid before administration of the antifolate, basically.
Q. Okay. So I noticed that the claim talks about reducing the toxicity of a GAR transformylase inhibitor, and you said that is a GARFT inhibitor?
A. Yes.
Q. Is pemetrexed a GARFT inhibitor?
A. Yes.
Q. How do you know that pemetrexed is a GARFT inhibitor?
A. Well, there's abundant prior art, but this was first reported by Shih, one of the co-inventors of the '974 patent.
Q. Before we turn to a publication by Shih, let's just take a look again at the cover page of the '974 patent. Who are the

named inventors on the '974 patent?
A. The named inventors on the '974 patent are Grindey and Shih.
Q. Okay. And let's turn now to Trial Exhibit 1087, if we could. Is this the article by Shih that you were referring to?
A. Yes.
Q. And where is this article by Dr. Shih published?
A. This article was published in *Cancer Research* in 1997.
Q. And what is the Shih paper generally about?
A. The Shih paper is generally about identification of the targets of pemetrexed.
Q. And what does it say about pemetrexed's inhibition of GARFT?
A. The paper explicitly states, "We now report that LY231514," that is pemetrexed, "and its polyglutamates, also markedly inhibit other key folate-requiring enzymes, including dihydrofolate reductase and GARFT."
Q. Okay. Now, if we go back for a moment to the '974 patent at Trial Exhibit 916 and look again at Claim 16, you also mentioned that it covers administration of an antifolate which binds to a folate-binding protein. And can you just remind the Court again what that means? What is the folate-binding protein?
A. A folate-binding protein is one of the transporters for

folates and antifolates.
Q. And is pemetrexed an antifolate that binds to the folate-binding protein?
A. Yes.
Q. How do you know that?
A. I know that from a paper by Westerhof.
Q. Could you turn in your binder to Trial Exhibit 918, please?
Is this the paper by Westerhof that you were referring to?
A. Yes, it is.
Q. And where was this paper published?
A. This paper was published in *Molecular Pharmacology* in 1995.
Q. And what is this paper generally about?
A. This paper is generally about the transport of a number of different folate antagonists, including pemetrexed.
Q. And what does it say about the transport of pemetrexed in particular?
A. It specifically states that pemetrexed was transported by both of the transporters that I mentioned earlier this morning, both the reduced folate carrier and the folate-binding protein.
Q. So in view of the Shih paper at Trial Exhibit 1087 that we looked at before and the Westerhof paper at Trial Exhibit 918,

what does Lilly's prior art '974 patent tell the person of ordinary skill in the art about folic acid pretreatment with pemetrexed?
A. The -- the person of ordinary skill in the art is taught that one can utilize folic acid pretreatment to reduce the toxicity of pemetrexed.
Q. And what does the '974 patent say about the use of folic acid pretreatment in terms of efficacy?
A. The '974 patent tells -- teaches that the -- that folic acid pretreatment, in combination with an antifolate, will reduce toxicity without adversely affecting therapeutic efficacy.
Q. And where do you see that in the '974 patent?
A. It is highlighted on the screen, and that comes from the background of the invention, Column 1, line 46 or 47 -- 47, I believe.
Q. Okay. Now, Dr. Ratain, are you familiar with the concept of leucovorin rescue with the antifolate methotrexate?
A. Yes.
Q. What is leucovorin?
A. Leucovorin is one of the reduced folates we heard about this morning. It's also known as folinic acid.
Q. And what is the concept of leucovorin rescue?
A. Leucovorin rescue is a completely different strategy. It's a -- it's a concept that was very innovative and was --

the concept was that one could give lethal doses of methotrexate if one came in with an antidote after a period of time after starting methotrexate. So the concept is you start the methotrexate, you give these doses of methotrexate that require, absolutely require you to give the rescue, and then once you give the rescue, the patient is generally protected from the side effects of the methotrexate.

Q. Does the goal of leucovorin rescue with that high dose of methotrexate differ from that of folic acid pretreatment with other antifolates?

A. Absolutely. It's like night and day.

Q. Can you explain what you mean?

A. Well, when we give, when -- the use of folic acid supplementation in low doses is simply to eliminate nutritional deficiencies, even nutritional deficiencies that are unrecognized, so that all patients have about the same amount of folic acid, or at least patients don't have folic acid deficiency. Whereas, leucovorin rescue is a therapeutic strategy only performed in the context of these lethal doses of methotrexate.

Q. Are there any other differences from a practical standpoint between leucovorin and folic acid?

A. Well, yes. Folic acid, particularly in the low doses claimed in the '209 patent, is readily available over the counter as part of standard multivitamin supplements, whereas

leucovorin, folinic acid, requires a prescription, and is very expensive and even recently has been in short supply.
Q. So if the goal of a person of ordinary skill in the art in June 1999 was to remedy a nutritional deficiency to address toxicity of an antifolate like pemetrexed, would leucovorin rescue have been the preferred approach?
A. Absolutely not.
Q. Why not?
A. Well, for all the reasons I just mentioned. Furthermore, Morgan -- Dr. Morgan, who we'll be hearing from later this week, I presume -- Dr. Morgan had previously demonstrated, for example, in conjunction with methotrexate that leucovorin blocked the efficacy of methotrexate in patients with rheumatoid arthritis.
Q. Was folic acid pretreatment ever actually used with pemetrexed itself?
A. Yes.
Q. And is there literature reporting on the use of folic acid pretreatment with pemetrexed?
A. Yes.
Q. What literature was there?
A. Well, there's both a preclinical study published by Worzalla, and then there's two abstracts published by Hammond from the Phase 1 clinical trial.
Q. Okay. Let's start with the preclinical publication by

Worzalla. If you could turn to Trial Exhibit 384, please.

Is this the Worzalla reference that you were referring to?

A. Yes.

Q. Where was this article published?

A. This article was published in *Anti-Cancer Research* in 1998.

Q. Okay. I want to pause for a little bit on this reference, and I want to start just by talking generally about the paper. What is the paper generally about?

A. Well, it's a paper generally about the use of folic acid in modulating the toxicity and efficacy of pemetrexed; and it's authored by three then Lilly employees, including Dr. Shih, one of the inventors of the '974 patent.

Q. And what's the background research that led to the study that was conducted in Worzalla?

A. Well, the background is described in the beginning of the paper, the introduction to the paper; and it's building upon prior work that had been performed by both Lilly and others in combining folates with antifolates. And specifically, the first sentence states, "Several animal studies have indicated that folic acid supplementation in combination with antifolate cancer therapy can prevent delayed toxicity and enhance the therapeutic potential of the GARFT inhibitor, lometrexol, and the TS inhibitor 1843U89."

Q. What other background information led to this Worzalla study?
A. Well, then the authors go on to cite the clinical work with lometrexol as well as Dr. Morgan's work with folic acid and rheumatoid arthritis. Specifically, they state, "Additional clinical studies demonstrated the protective effects of folic acid against lometrexol toxicity in humans. Morgan and co-workers concluded that a daily supplement of one milligram of folic acid during low-dose methotrexate therapy in patients with rheumatoid arthritis was useful in lessening toxicity without altering efficacy."
Q. And that's at page 3235 of this exhibit?
A. Yes.
Q. Okay. Who is Dr. Morgan?
A. Dr. Morgan is a physician and nutritional expert at the University of Alabama.
Q. And what is her area of expertise?
A. Her major area of expertise, as I said, is the interface of nutrition and medicine.
Q. And what work is being cited here as relevant to the -- to the study that Dr. Worzalla is conducting?
A. This reference 10 in this paper here is her seminal paper published in the *Annals of Internal Medicine*.
Q. And in the 1990s, were you familiar with the work that Dr. Morgan did that -- that's being referred to here?

A. Yes. She published it in journals that I subscribe to and read, because I belong to the organizations that publish them.
Q. Okay. Let's talk about the study that was conducted in the Worzalla paper itself. What model is being used here to assess the effect of folic acid?
A. This is an animal model of cancer, the type of lymphoma model.
Q. What animal was being used?
A. This was in mice.
Q. In mice. Can you explain what the study groups of mice were that were used to assess the effect of folic acid?
A. Well, this was a nicely-designed study to address the question of how folate in the diet affects the toxicity and efficacy of pemetrexed, as well as how folic acid supplementation affects the activity and toxicity of pemetrexed.

And thus, there were three groups of mice that were evaluated and compared. There was the low-folate-diet group, mice that received a diet that essentially was devoid of folate; a similar group of mice, but who also received folic acid supplementation; and then there was another group of mice that just got plain old, normal mouse chow.

Q. And what tests did the authors run on these three groups of mice?
A. Well, they were testing for both the antitumor activity,

the effect of the pemetrexed on the cancer as measured by percent tumor inhibition, as well as the toxicity of the drug, defined as the percentage of mice that died.

Q. And were the results of these experiments reported in the paper?

A. Yes.

Q. Let's take a look at page 3237 of the article. And can you tell us what results were reported for the group of mice on the low-folate diet?

A. Well, it stated explicitly in the paper, on page 3237, "For mice on low-folate diet, pemetrexed at 0.3 and 1 milligram per kilogram per day produced 100 percent inhibition of tumor growth for tumors measured one day after the completion of a single course of drug treatment. As noted in Figure 1, higher drug levels yielded unacceptable toxicity."

Q. So generally speaking, then, what were the results reported for the low-folate-diet mice?

A. Well, to summarize this more simply, what they showed was that these mice were very sensitive to the drug, as well as the tumor was very sensitive to the drug, so that at very low doses, there was benefit; but once you got up into what I would call moderate doses, these mice died.

Q. Okay. And staying on that same page, what results were reported for the mice who were in the low-folate-diet-but-got-folate-supplementation group?

A. Well -- and, again I'm going to first read right from the paper; and then I'll talk about my interpretation of it.

"From mice on low-folate diet that received a folate supplement of 15 milligrams per kilogram per day by oral gavage" -- oral gavage is sort of force feeding of the mouse -- "significant inhibition of tumor growth was noted over a broad dose range, 10 to 1,000 milligram per kilogram per dose.

"Moreover, 100 percent inhibition of tumor growth was observed at 30 to 1,000 milligrams per kilogram per dose without any lethality."

Q. Okay. And so in your own words, what is this article reporting about the results that were seen for the low-folate-plus-folic-acid-supplementation mice?

A. Well, my kids would probably say these mice were invincible. There was just -- you could give them extraordinary amounts of drug, and you could achieve 100 percent inhibition of tumor growth.

Q. What about the lethality that was reported or the toxicity that was reported with respect to these mice?

A. There was no lethality. These were super mice.

Q. Okay. And then on that, staying on the same page, what results were reported for the group of mice on the standard diet?

A. Well, what's reported for the mice on the standard diet,

this antitumor dose response with folate supplementation was virtually identical to that observed for mice receiving the standard diet. So, what it's saying now, it's just finished telling us about the super mice; and now it says the dose response was the same as the mice on the standard diet. However, the lethality was significantly greater for the mice on the standard diet.

Q. Okay. And when it says that the antitumor dose response for this group of standard mice was virtually identical, what measure is it talking about there? What is the antitumor dose response?

A. The antitumor dose response is the percent inhibition as a function of dose.

Q. Okay. And that's the inhibition of tumor?

A. That's the inhibition of tumor, yes. And it's stating it was virtually identical.

Q. What does it report about the lethality or toxicity of the mice on the standard diet?

A. The mice on the standard diet had 100 percent lethality at a dose of 800 milligram per kilogram per day and a 10 percent lethality at a dose of 400 milligram per kilogram per day.

Q. Okay. Now, is there a figure in the Worzalla paper that reports on the activity and toxicity data for all three of these groups?

A. No.

Q. Is there a figure that reports at least some of the data for these groups of mice?
A. Yes.
Q. What figure is that?
A. Figure 2.
Q. Okay. So if we take a look at Figure 2 -- and that's on page 3238 of Trial Exhibit 384 -- can you explain what's reported in Figure 2 with reference to both the X and Y axes here?
A. Yes. This is a bit of a complicated figure. And so let me first orient the Court to the axes. So, on the X axes, we see drug dosage and milligrams per kilogram on a log scale so that the same distance from 1 to 10 is from 10 to 100.

And then we have two different things plotted on the Y axis. We have solid lines that represent percent inhibition, and that's activity; and we have dotted lines that represent percent lethality. That's toxicity.
Q. Okay. And so for which of the three groups of mice that we just discussed, for which of those is there data that's represented in Figure 2?
A. The data that are reported here are for the mice on the low-folate diet, and then for the mice on the low-folate diet with the folate supplementation.
Q. Is there data reported in Figure 2 for the mice on the standard diet?

A. No.
Q. Now, would a person of ordinary skill in the art ignore the data with respect to the standard diet simply because it's not represented in Figure 2?
A. No. It's plainly stated in the text of the manuscript.
Q. Now, I would like to just have you explain Figure 2 in a little bit more detail. Can you -- have you prepared a graphic to show what Figure 2 shows just for the low-folate-diet group?
A. Yes, I have.
Q. Okay. Is this that graphic?
A. This is that graphic.
Q. Okay. So, can you, again, explain with reference to the lines that you've put on this graphic what Figure 2 is reporting about the low-folate-diet group?
A. Okay. Up at the top left, with the triangles, shows the percent inhibition, which is 100 percent for the low-folate-diet group mice, and one can see that this activity was obtained at a very low dosage of pemetrexed, dosages of 1 milligram per kilogram and less.
Q. Okay. And what does your figure show about the lethality or toxicity of the low-folate-diet group?
A. Well, the lethality is shown as the vertical purple bars; and one can see that there's lethality at doses of 3 milligram per kilogram and up, with 100 percent lethality at

30 milligrams per kilogram.
Q. Have you also prepared a slide to show the data on Figure 2 for the low-folate diet plus folic-acid-supplementation group?
A. Yes, I have.
Q. Okay. Can we have the next slide?
Okay, looking at Slide 69, can you explain what this data shows for the low-folate diet plus folic-acid-supplementation group of mice?
A. Yes. First of all, there's the plot of the activity, which is shown as the red circles with the solid lines. And one can see that there's activity of the drug at doses of 3 milligram per kilogram and up; and when one gets to doses of about 30 milligram per kilogram, there's 100 percent inhibition. In other words, the perfect activity.
Q. And where do you see on this figure the data for percent lethality or toxicity in this group of low-folate diet plus folic-acid-supplemented group?
A. Well, as I mentioned earlier, these are the invincible mice; and it's hard to see the lethality because it's zero. But there are little bars plotted at the zero line for the lethality for these mice.
Q. Now, I know you said earlier that the standard-diet group data isn't plotted in Figure 2, but is there information in the -- reported in the Worzalla article that gives you enough

information to plot that information on Figure 2?
A. Yes. The -- if you go back to page 3237, there's a statement, "This antitumor dose response with folate supplementation" -- so that's the group we were just looking at -- "was virtually identical to that observed for mice receiving standard diet."

So a person of ordinary skill in the art would read that, that the antitumor dose response for the low-folate diet with folate supplementation is virtually identical to mice receiving a standard diet.

Q. And so have you prepared a graphic plotting what the standard diet data would look like if it were plotted on a figure similar to Figure 2?
A. Yes. I made the assumption that virtually identical meant the same as identical; and therefore, I plotted that the dose response for the standard-diet group was the same dose response as for the low-folate-diet group with folate supplementation.

MR. PERLMAN: Your Honor, you indicated at the pretrial conference, you would be taking the demonstrative back with you after the testimony. I understand this is not data actually in the patent, but the doctor's testimony regarding how he prepared this demonstrative is in the record.

I think it would be appropriate, so the record doesn't become confused later, that we note the slide number

where it is not data actually in the article but the doctor's opinion regarding what the data would look like if it were plotted so that we don't have confusion about whether this is actual data or the doctor's understanding of what it means to have virtually identical data.

I don't have an objection to the use of the demonstrative with the understanding of what it is, but I am concerned that as the months go by, we may lose track of this; and there's no number of the slide in the record.

MS. RAPALINO: Sure. I can just say the number of the slide if that helps. I think the testimony is clear as to which testimony he's plotting here, but we can just put the number in if that helps.

THE COURT: That would help.

BY MS. RAPALINO:

Q. So, is Slide 60 the graphic you've prepared showing how a person of skill in the art would understand the standard diet?

THE COURT: Counsel is standing again.

MR. PERLMAN: It's number 70 on my screen. I just want to make sure that we don't mess this up.

MS. RAPALINO: I think that's why I said Slide 70.

THE COURT: You said 60.

MS. RAPALINO: I'm sorry. It's Slide 70, the graphic.

MR. PERLMAN: On this occasion, I was trying to

help.

MS. RAPALINO: My apologies. It's Slide 70.

THE COURT: 70.

MS. RAPALINO: I think I'm just not capable of saying the number 70.

BY MS. RAPALINO:

Q. Is Slide 70 a graphic you've prepared showing how a person of ordinary skill in the art would plot the data for the standard-diet group on a figure similar to Figure 2?

A. Yes. And as I said, I took the authors at their word, that virtually identical was identical; and therefore, I plotted the same dose response for the standard-diet group as for the low-folate-diet group with folate supplementation.

Q. Okay. And could we go back to Slide 70? There we go.

Can you explain with reference to your graphic at Slide 70 what this data reflects with respect to the standard-diet group of mice?

A. Well, it reflects the -- both the percent inhibition for the standard-dose group -- standard-diet group of mice as well as the percent lethality for the standard-diet group of mice by dose.

Q. And which line represents the antitumor inhibition data for the standard-diet group?

A. That's the blue squares and the solid line.

Q. And where is the data for the percent lethality or

toxicity for the standard-diet group of mice?
A. The percent lethality is depicted in the blue vertical bars at the right side of the slide, and it's based on data in the text that shows that at a dose of 400 milligram per kilogram per day, there's 10 percent lethality; and at a dose of 800 milligram per kilogram per day, there's 100 percent lethality.
Q. Now, have you prepared a graphic that shows what the data for all three of the mice, the treatment -- the mice group, groups would look like?
A. Yes, I have.
Q. Can we see that graphic? Okay. Is Slide 72 that graphic?
A. Yes.
Q. Okay. And can you explain what we see when we look at the comparison of all three groups in terms of their activity data or percent inhibition of tumor data and their lethality or toxicity data?
A. Yes. Here one sees all three groups together. What one sees is the mice that were on the low-folate diet had 100 percent inhibition at very low doses, but also were extremely sensitive to the toxicity.
Q. Is that the purple lines on your figure?
A. These are the purple lines and purple triangles, yes.
And then the other groups of mice had the same percent inhibition based on the phrase in the manuscript

itself, virtually identical; but the mice that were on the standard diet had significant toxicity beginning at doses of 400 milligram per kilogram per day, whereas the mice with the folic acid supplementation had no lethality whatsoever.

Q. Now, do you have a slide that shows -- that separates out the data for activity or percent inhibition, the antitumor activity from the lethality or toxicity data?

A. Yes, I do.

Q. And can you explain what's shown here?

A. Yes. So, on the left is the activity percent inhibition, and on the right is the percent lethality, the toxicity.

Q. And for the record, this is Slide 73?

A. Yes.

Q. Okay. And so can you explain what you see when you look at the slide on the left with respect to percent inhibition or antitumor activity for each of the three groups of mice?

A. Well, when you look at the antitumor activity in the slide, it looks like there's essentially two groups. There's a group that has 100 percent inhibition at low doses, and then the remaining animals had 100 percent inhibition at significantly higher doses.

Q. And then what information does the toxicity data on the right-hand side add with respect to the three groups?

A. Well, on the toxicity data, what one sees is that the mice that were on the low-folate diet were very sensitive to the

drug and began dying at very modest doses of the drug. The mice on the standard diet were relatively resistant to the lethality of the drug, with no lethality until you get to 400 milligram per kilogram per day, whereas the mice on the low-folate diet plus folic acid were resistant to the lethal effects of pemetrexed.

Q. Now, what conclusions would a person of ordinary skill in the art draw from these data, comparing all three groups of mice?

A. A person of ordinary skill in the art, looking at all three groups of mice, would understand that the mice that did the best were the mice that received the folic acid supplementation.

Q. And then what would they conclude, then, from the comparison of all three groups about the effects of folic acid supplementation?

A. What a person of ordinary skill in the art would conclude was that folic acid supplementation markedly reduced the toxicity of pemetrexed while maintaining antitumor activity.

Q. And did the authors draw any conclusions about the comparison of the low-folate diet plus folic-acid-supplementation group as compared to the standard-diet group?

A. Yes, they did.

Q. And what conclusion did they draw?

A. They concluded, "However, low-folate-diet animals with high levels of folate supplementation demonstrated decreased lethality to pemetrexed compared to conventional-diet animals, suggesting that folate intake can be manipulated to achieve greater therapeutic effects," which is basically what I just said.

Q. And when they say that folate intake can be manipulated to achieve greater therapeutic effect, is that correct based on the data that you analyzed?

A. Yes.

Q. How so?

A. What they mean by manipulate is, you can get folic acid supplementation. The folic acid supplementation allows you to improve the therapeutic index of pemetrexed.

Q. Did you prepare another graphic that specifically compares the low-folate diet plus folic acid group to the standard-diet group?

A. Yes, I did.

Q. And what do you see -- can you explain what you see when you do this comparison of just the standard-diet group to the low-folate diet plus folic-acid group? And this is at Slide 76.

A. When one compares the standard-diet group versus the low-folate diet plus folic-acid group, one has exactly the same therapeutic effect, the antitumor effect, virtually

identical. Even if we were to draw this differently, we could draw it any way we like as long as we would agree that dose response is virtually identical.

But, what one sees is that the percent lethality is only present in the standard diet. There's absolutely no lethality at all in the mice who receive folic acid supplementation.

Q. Did you prepare a slide where you have broken out the activity data again from the toxicity data?

A. Yes, I have.

Q. And this is at Slide 77. Can you explain what's shown here?

A. Again, on the left we have the antitumor activity, the percent inhibition; and this slide is drawn to reflect what is stated in the text of the Worzalla paper, that the dose response curve, which is what we're looking at, dose versus response percent inhibition, is virtually identical between standard diet and low-folate diet with folic acid supplementation.

Q. And what do you see when you compare the toxicity or lethality of the two groups, the standard-diet group and the low-folate diet plus folic acid supplementation?

A. Well, you see marked contrast in the lethality between these two groups. One could say it's like night and day in that there's absolutely no lethality whatsoever with the folic

acid supplementation; but with the standard diet, there is a 100 percent lethality at a dose of 800 and detectable lethality at 400.

Q. Do the standard-diet mice and the low-folate-diet mice with folic acid supplementation have the same amount of folic acid?

A. No. The low-folate diet plus folic-acid mice have more folic acid than the standard-diet mice.

Q. So, going back to this comparison of the standard-diet group to the low-folate diet plus folic acid group, what does this tell you about the therapeutic index when -- with folic acid supplementation?

A. Well, I want to remind the Court that therapeutic index is the concept, the ratio of benefit to risk. We're told by the authors of the paper that the benefit is the same in the two groups, and it's clear that the toxicity is different between the two groups. And the worse toxicity is with the standard diet; and therefore, the therapeutic index is significantly better for the group that received the folic acid supplementation.

Q. So what would a person of ordinary skill in the art understand about the relative therapeutic index of the low-folate diet plus folic-acid-supplementation group?

A. The person of ordinary skill in the art would conclude exactly what I've been saying. Folic acid supplementation was

demonstrated to preserve the antitumor activity of pemetrexed while reducing toxicity.

Q. Are you aware of any characterizations by Lilly of the Worzalla data?

A. Yes, I am.

Q. And what are you aware of?

A. I'm aware of communications they had with the Food & Drug Administration regarding this same data set.

MR. PERLMAN: Objection. Those communications postdate the priority date and they are not public, and so they would not have been available to the person of ordinary skill in the art. And so however Lilly characterized this document after the fact in nonpublic communications cannot be relevant to the obviousness inquiry.

MS. RAPALINO: The doctor's testimony will make clear the relevance of the documents. It's not about how a person of ordinary skill in the art would understand the data.

THE COURT: Well, how will it be relevant?

MS. RAPALINO: If I can elicit the testimony from Dr. Ratain, he's just going to testify about how the interpretation -- Lilly's interpretation of the data in Worzalla is consistent with his own interpretation and with the interpretation of how a person of ordinary skill in the art would see it.

MR. PERLMAN: Your Honor, that's not medical

expertise. That's not from the perspective of the person of ordinary skill. That's using the witness as a foil for closing argument.

THE COURT: I'll sustain the objection. This was after.

MS. RAPALINO: Okay.

THE COURT: Okay?

BY MS. RAPALINO:

Q. Let's go back to the Worzalla paper itself, if you could look at page 3238. What does the Worzalla paper itself say with respect to the future development of pemetrexed based on these data?

A. Basically, the last sentence of this paper, which begins on 3238 and ends on 3239, states, "The combination of folic acid with pemetrexed may provide a mechanism for enhanced clinical antitumor selectivity."

Q. And so, what does that mean?

A. What that means is that the authors are stating that this is an exciting approach that may result in clinical benefit, in other words, benefit in patients, using this combination of folic acid pretreatment followed by pemetrexed.

Q. Were such clinical trials ever carried out as of June 1999 with pemetrexed and folic acid?

A. Yes.

Q. And were those -- were there reports in the literature of

clinical trials with pemetrexed and folic acid pretreatment?
A. Yes. There were two abstracts by Hammond.
Q. Okay. Could you turn in your trial exhibit binder, please, to Trial Exhibits 911 and 912?
And if you look at Trial Exhibit 911 at page Bates No. 476, Abstract 620P, is this one of the Hammond abstracts that you were referring to?
A. Yes, it is.
Q. And if you turn to Trial Exhibit 912, Abstract No. 866, is that the other Hammond abstract you were referring to?
A. Yes.
Q. Let's start with the second one at Trial Exhibit 912. Where was this abstract published?
A. This abstract was published as part of the proceedings of the 1998 ASCO meeting.
Q. And is that an important meeting?
A. Yes. As I mentioned previously, ASCO is the premier international clinical oncology society, and this was a very large meeting.
Q. And can you explain what an "abstract" is?
A. Well, an "abstract" is conceptually, essentially, an application for presentation of a study at a meeting.
Q. Okay. What's being reported in -- or what was this Phase 1 study that's reported in this Hammond abstract designed to test?

A. This study was specifically designed to test whether administering folic acid pretreatment with pemetrexed would permit the ability to administer higher doses of pemetrexed that had been previously tolerated in the absence of folic acid pretreatment.
Q. Can you describe what was done in this study with respect to the dose of folic acid and the schedule?
A. Yes. Folic acid was administered at five milligrams daily for five days starting two days before pemetrexed.
Q. And how many treatment -- how many patients were enrolled in this study?
A. Well, at the time that this abstract was submitted, there had been 21 patients that had been enrolled.
Q. And could you read aloud the conclusion in the last sentence of this Hammond abstract?
A. The conclusion is "These results indicate that folic acid supplementation appears to permit pemetrexed dose escalation."
Q. What would a person of ordinary skill in the art as of June 1999 understand from this conclusion?
A. A person of ordinary skill in the art would agree with the conclusion of the authors, and would understand that folic acid supplementation reduced the toxicity of pemetrexed.
Q. Okay. Let's turn back to the other Hammond abstract at Trial Exhibit 911, and again, it's at Bates No. 4776, Abstract No. 620P. Where was this abstract published?

A. This abstract was published as a supplement to *Annals of Oncology*, which is the journal published by the European Society of Medical Oncology.
Q. And was this also in preparation for a meeting?
A. Yes. This was the abstract from that society's meeting, what we call ESMO.
Q. And is that an important meeting in oncology?
A. Yes. That's the major European meeting in oncology.
Q. Would a person of ordinary skill in the art have been aware of that meeting?
A. Yes.
Q. Now, is this reporting on the same study that as the other abstract we just looked at?
A. Yes, it is.
Q. So could you read aloud the conclusion in this Hammond abstract?
A. The conclusion is that "Folic acid supplementation appears to permit pemetrexed dose escalation by ameliorating toxicity."
Q. And what would a person of ordinary skill in the art in 1999 have understood from that conclusion?
A. I think a person of ordinary skill in the art would understand the same thing that's stated there, that folic acid supplementation reduces the toxicity of pemetrexed.
Q. Was the Phase 1 study in the Hammond report, in these

Hammond abstracts, designed to test the efficacy of pemetrexed with folic acid pretreatment?
A. No.
Q. Why not?
A. Because Phase 1 studies do not test efficacy. The purpose of these studies was to address the pharmacologic question to see if one could demonstrate the same results that one had previously demonstrated in Worzalla, that one could safely administer higher doses of pemetrexed in the context of folic acid pretreatment.
Q. Now, even if it's not designed to test for the efficacy, is there any signal in either of the Hammond abstracts that there was any therapeutic benefit from the folic acid regimen with pemetrexed that's described in these abstracts?
A. Yes. If we go back to the ASCO Abstract, Exhibit 912, there was a partial response observed in a patient with metastatic colon cancer. This is a patient that would have had lots and lots of prior chemotherapy prior to going onto this Phase 1 study.
Q. So, would you say that the treatment regimen in the Hammond abstracts provided a therapeutic benefit?
A. Yes.
Q. And what would a person of ordinary skill in the art understand from reading the two Hammond abstracts?
A. A person of ordinary skill in the art from reading the two

Hammond abstracts would understand that number one, folic acid supplementation reduced the toxicity of pemetrexed; and number two, folic acid supplementation with pemetrexed still allowed -- still provided therapeutic benefit.

Q. Okay. I'd like to move on now to talk about the third category of information that you said was taught by the prior art as of June 1999. And that's that poor nutrition predicts the toxicity of chemotherapy, including antifolates generally and pemetrexed in particular. What were some nutritional measures that predicted antifolate toxicity as of June 1999?

A. Well, the major predictor of antifolate toxicity that had been reported and described in the literature was homocysteine.

Q. And can you just briefly remind the Court what homocysteine is?

A. Homocysteine is a blood marker that indicates that there's -- suggests that there's a nutritional deficiency of a vitamin, usually folate or B12, but also potentially another vitamin, B6.

Q. For which antifolates have there been reports of homocysteine as a predictor of toxicity?

A. Well, Morgan had done studies of homocysteine levels and the association with toxicity of methotrexate, and there are also prior art references regarding the association of

homocysteine levels prior to treatment as being associated with the toxicity of pemetrexed.

Q. Okay. I'd like to focus on those reports about the level of homocysteine being correlated with pemetrexed toxicity. Which prior art references were there that taught about that correlation between elevated homocysteine and toxicity of pemetrexed?

A. Well, there are two abstracts by Niyikiza, and then there are also some references to this work in two articles by Calvert.

Q. Okay. I'd like to turn to Trial Exhibit 911 again. And if you could look at Bates No. 473, Abstract No. 609P. Is this one of the abstracts by Dr. Niyikiza?

A. Yes.

Q. And --

MR. PERLMAN: Your Honor, can I state something to aside confusion later? One of the Hammond abstracts and one of the Niyikiza abstracts are in the same physical document. So they're both going to be Exhibit 911.

Ms. Rapalino just transitioned to it, but I found myself confused by it over the weekend, so I thought I would put on the transcript that fact so that we can avoid confusion later, because often in trials we assume that different documents have different numbers.

MS. RAPALINO: I can clarify that on the record as

well with the witness.

THE COURT: Okay. If you would, thank you.

BY MS. RAPALINO:

Q. Now, Dr. Ratain, where is this Niyikiza abstract published?

A. This is published in the same issue, the same supplement of *Annals of Oncology*, and it was presented in the same session as the Hammond abstract.

Q. And can you remind the Court what meeting this was for?

A. This was the 1998 ESMO meeting.

Q. Okay. Now, generally, what is the subject of this Niyikiza abstract?

A. It's generally about trying to understand predictors of pemetrexed toxicity.

Q. Now, I want to start by looking at the conclusion, and what were -- what was -- what was Dr. Niyikiza's conclusion in this abstract?

A. The major conclusions were "Toxicities resulting from treatment with pemetrexed appear to be predictable from pretreatment homocysteine levels. Elevated baseline homocysteine levels highly correlate with severe hematologic and nonhematologic toxicities following treatment with pemetrexed."

Q. Before we look at that in any more detail, let's also just look at Trial Exhibit 910. And I would point you there to

Bates No. 786 and to Abstract No. 2139. And is this the other Niyikiza abstract you referred to?
A. Yes. This one was presented at the ASCO meeting in the spring of 1998.
Q. And generally, what's the subject of this Niyikiza abstract?
A. It's the same as the other Niyikiza abstract.
Q. And again, if we could just go to the conclusion in this paper, what does this abstract conclude about the correlation between homocysteine and toxicity of pemetrexed?
A. I would describe this more as the results, because it's in the middle of the abstract, but it basically states there was a strong correlation between baseline homocysteine levels and the development of the following toxicities at any time during the study. And then it goes through and notes neutropenia. This is a decrease in the white blood cells that fight infection; thrombocytopenia, a decrease in the blood cells that clot the blood; mucositis, which is mouth sores; and diarrhea.
Q. Okay. And if we look at the title of this Niyikiza abstract, it says "Relation of vitamin metabolite profile to toxicity." Which vitamin metabolites are being looked at in these Niyikiza abstracts?
A. Well, the investigators looked at three different chemicals in the blood. They looked at homocysteine,

cystathionine and methylmalonic acid.
Q. Can you just remind the Court what methylmalonic acid is?
A. Methylmalonic acid is elevated in patients with B12 deficiency.
Q. Now, what kind of study did Dr. Niyikiza do to determine the relationship between these vitamin metabolite profiles and toxicity?
A. This was a multivariate statistical analysis.
Q. Have you ever conducted a multivariate statistical analysis?
A. Yes.
Q. How many times?
A. Too many to count.
Q. So are you familiar with how such an analysis is conducted?
A. Yes, I am.
Q. And are you familiar with how to interpret the results of such an analysis?
A. Yes, I am.
Q. Now, if you look at the Niyikiza abstract at Trial Exhibit 910, there's a statement in there that says, "No correlation between toxicity and the remaining prespecified predictors was seen." Do you see that?
A. I do.
Q. Now, does that mean that a person of ordinary skill in the

art would have concluded definitively that there was no correlation between MMA levels and toxicity?
A. No.
Q. Can you explain why not?
A. What one can conclude is that the information regarding the toxicity was captured by the homocysteine levels. And so that any variable that might be correlated with the homocysteine wouldn't add any information.
Q. Is there any evidence that MMA levels are correlated themselves with homocysteine levels?
A. Yes. Homocysteine and MMA levels are known to be correlated, particularly in patients with B12 deficiency.
Q. Okay. And can you explain in a little bit more detail why it is that if MMA levels and homocysteine levels are themselves correlated, you wouldn't see a correlation between MMA and toxicity, even if there were such a correlation?
A. Well, let me explain this in a way that I often use for teaching my junior trainees. So, let's just say one wanted to do a study of the relationship of foot length to height. And one had data for right foot length, left foot length and height.

And you said, "Well, let's do a multivariate correlation." And just as background, usually in right-handed people, the left foot is a little bigger than the right, and in left-handed people, the right foot's a little bigger than

the left. So they're not perfectly the same.

If you did a multivariate analysis, you would, depending on the way the numbers fell out, you would either find that right foot was correlated with height or left foot length was correlated with height, but never in a multivariate analysis would you find that measuring the length of both feet gives you additional information.

Q. Okay. And why is that?

A. That's because there's just -- they're so tightly correlated, you capture no additional information from knowing the length of both the right foot and the length of the left foot when you already know the length of one of the two feet.

Q. Okay. So in your analogy, as it relates to this case, what's equivalent here to the right foot and the left foot?

A. It's MMA and homocysteine are kind of like right foot and left foot.

Q. And what would be equivalent here to height?

A. And height would be toxicity.

Q. Okay. So, in the Niyikiza abstract where it says that no correlation was seen between MMA levels and toxicity, what would that mean to a person of ordinary skill in the art in the context of this multivariate analysis?

A. A person of ordinary skill in the art who understood and read the abstract, and saw that a multivariate analysis was performed, would understand that there's a correlation between

homocysteine levels and toxicity, but would not understand whether or not there was a correlation between any of the other variables and toxicity. One just wouldn't know one way or another.

Q. So what would the person of ordinary skill in the art take away from the Niyikiza abstracts with respect to MMA levels in vitamin B12?

A. One would not know one way or the other whether the elevated homocysteine represented folate deficiency, B12 deficiency, or both folate and B12 deficiency.

Q. And so what would the person of skill in the art conclude, then, based on the Niyikiza abstracts?

A. A person of ordinary skill in the art would conclude that a deficiency of folate and/or B12 was associated with the toxicity of pemetrexed.

Q. Now, you mentioned that there were other references that discuss this correlation between homocysteine levels and toxicity from pemetrexed. What are some other examples of references that talk about that?

A. Well, this -- these abstracts were cited repeatedly by Lilly authors and Lilly investigators, and I noted that it was -- this has been cited in a couple papers by Calvert.

Q. Okay. Let's take a look at Trial Exhibit 401.

Is this one of the papers by Dr. Calvert that discusses the Niyikiza study?

A. Yes.
Q. And where was this article published?
A. This is the first paper, the introductory paper in the issue that resulted from the Ixtapa, Mexico meeting in seminars in oncology.
Q. And what does Dr. Calvert say in this article about the Niyikiza study and the correlation between homocysteine and toxicity?
A. This is described on page -- let's see, I'm having trouble seeing the page.

It's Bates 155869. "The measurement of pretreatment plasma homocysteine has proved to be a sensitive way of predicting the toxicity of pemetrexed." And then cites Reference 17, which is the Niyikiza ASCO abstract we were just looking at.
Q. Okay. And then if you turn to Trial Exhibit 907, can you remind the Court again just what this trial exhibit is?
A. This Trial Exhibit 907 is the concluding article, summary and conclusions from the Ixtapa issue.
Q. And if you look at page 106 of this article, what is Dr. Calvert saying here about the Niyikiza study and the correlation between homocysteine and toxicity?
A. He states "The recently presented study of the use of plasma homocysteine as a marker for folate deficiency shows a correlation between elevated pretreatment homocysteine levels

and the subsequent occurrence of Grade 3 or 4 toxicity." And then Reference 418 is the same ASCO abstract we were just looking at.

Q. So what would the combination of these Niyikiza abstracts and these Calvert articles citing to the Niyikiza abstracts, what would all of this tell a person of ordinary skill in the art as of June 1999?

A. These would -- all of these articles and abstracts would teach a person of ordinary skill in the art that homocysteine is associated with pemetrexed toxicity, and that the higher the homocysteine, the greater the probability or severity of pemetrexed toxicity.

Q. Okay. I'd like to move on now to talk about the fourth category of information.

THE COURT: Counsel, why don't we take our afternoon break. The court reporter needs a break every hour and 45 minutes for his fingers.

MS. RAPALINO: Absolutely. No problem. Thank you, Your Honor.

THE COURT: We'll take a 15-minute break and then we'll talk about the next slide.

THE COURTROOM DEPUTY: All rise.

(Recess at 2:50, until 3:11)

THE COURT: We're back on the record. And you may continue, Counsel.

MS. RAPALINO: Thank you, Your Honor. Before I continue, I just respectfully wanted to ask the Court for some clarification about the basis for your earlier ruling on an objection by Mr. Perlman, just because it will implicate other -- potentially implicate other exhibits for use both with this witness and others. The exhibit at issue is an FDA correspondence with Eli Lilly back from around the time that the patent application was filed in 2000, and I just wanted to understand the basis for the ruling that --

THE COURT: What was your exhibit number?

MS. RAPALINO: It is Exhibit No. -- I believe it's -- is it 76? 76.

THE COURT: What was your objection again, Counsel? Because it's been a while since --

MR. PERLMAN: Yes. Your Honor, this is a document that was filed well after June 1999, which is the priority date. It is not a public document; it is a private communication between Eli Lilly and the FDA. It would not have been known to the person of ordinary skill in the art. It could not be relevant to the obviousness inquiry. And all that I believe counsel for the defendants are doing is they want to put Lilly's statement to the witness and have him make an argument that you would make in closing argument about he says what Lilly said, which is not expert testimony by a medical expert. It's not prior art, so it's not relevant to

obviousness. And so whether or not the document is admissible, it's not appropriate through this witness.

That is my objection.

THE COURT: Okay. So, that would have been a relevance objection, which the Court had sustained. And can you say how it would be relevant at this stage in the proceedings from this witness?

MS. RAPALINO: Yes. Just to be clear again, Dr. Ratain had already offered his argument about how a person of ordinary skill in the art would have interpreted a set of data, and this was just being offered as a contemporaneous document around the same time as the filing date about a characterization of the same objective body of data that Dr. Ratain had already formed his opinion about and just confirming that this was a reasonable interpretation of the data as of around the same time as the filing of the patent application.

MR. PERLMAN: And, Your Honor, that may be a perfectly fair argument for a posttrial brief or a closing argument, but it's not an appropriate use of this witness to use him as a foil to simply argue from documents that are not from the relevant time period and are not public and could not reflect what the person of ordinary skill --

THE COURT: You can't help her. Do you want to talk to your co-counsel?

MR. WIESEN: If I could, Your Honor.

THE COURT: You may.

MS. RAPALINO: Excuse me, Your Honor.

(Off the record.)

MS. RAPALINO: And I guess, Your Honor, I just wanted to seek clarification. Mr. Perlman offered several reasons for why this document isn't relevant, and I just wanted to understand which of those bases is the reason for excluding it. In other words, is it related to timing? Is it anything after the filing date of the patent isn't relevant? Is it the fact that it is a confidential communication? I just wanted to clarify that so I can apply that ruling consistently for other exhibits that may come up.

MR. PERLMAN: It's all of that, Your Honor. And they each independently and collectively form the basis of my objection, which was sustained, and I don't think the basis for Your Honor's ruling is especially ambiguous right now, and I don't know that I have anything more to say on the subject.

THE COURT: Okay.

All right. The objection remains sustained based upon relevance with respect to all of the matters argued by counsel.

MS. RAPALINO: Okay. And so just to be clear, any documents that are after the filing date of the patent-in-suit or are otherwise not -- or are not publicly available are

not -- will be considered deemed not relevant to the issue of obviousness?

THE COURT: No. If you have another one, you offer it, and we'll see if he objects.

MS. RAPALINO: Okay.

THE COURT: Okay?

BY MS. RAPALINO:

Q. Okay. Dr. Ratain, I want to continue where we left off and talk about the fourth category of information that you said was available as part of the state of the art as of June 1999, and that's that homocysteine was used as a marker for folate and vitamin B12 deficiency. We've heard a little bit about this today, but can you just explain again what you mean by that?

A. What I mean is that if one is going to consider using homocysteine to predict toxicity, one would -- a person of ordinary skill in the art would understand that the most common -- the most likely causes of that in this particular cancer population would be that the patients would have a vitamin deficiency and that vitamin deficiency could be folate deficiency or B12 deficiency.

Q. And was there prior art available as of June 1999 that reported on this correlation between -- or association between elevated homocysteine and a folate or a vitamin B12 deficiency?

A. Yes, there was.
Q. And what prior art is that?
A. Well, I think a really good piece of prior art is a 1993 paper by Allen.
Q. Could you turn in your binder to Trial Exhibit 502?
Is this the Allen paper that you're referring to?
A. Yes, it is.
Q. And who is Robert Allen?
A. Robert Allen is a physician and nutritional scientist at the University of Colorado who was also Dr. Niyikiza's collaborator and collaborated with other Lilly scientists on a number of other prior art documents.
Q. And where is this exhibit, this paper by Dr. Allen, Trial Exhibit 502, published?
A. It's published in a journal called *The FASEB*, F-A-S-E-B, *Journal* in 1993, and "*FASEB*" is the *Federation of American -- Federation for American* -- I'm blocking. I'm sorry.
Q. It's okay.
A. It's a long day.
Q. We can use the abbreviation; it's *The FASEB Journal*.
Now, is there anything in this paper by Dr. Allen about the use of homocysteine as an indicator of vitamin B12 or folate status?
A. Yes. This is a carefully written description of the use of the association of various so-called vitamin metabolites

and the relationship to folate deficiency and B12 deficiency.
Q. Could you turn in this exhibit to page -- Bates No. ending in 8997? I'm sorry. I have the wrong page number. It's 8999. And looking at Figure 4B, can you explain what this figure shows?
A. Yes. This is -- this Figure 4B of the Allen paper depicts homocysteine data, serum total homocysteine for 180 individuals. This includes 60 normal subjects, 60 patients that were documented to have B12 deficiency and were receiving B12 supplementation, 60 patients who were documented to have folate deficiency and receiving folate supplementation.
Q. And what does this show about the level of homocysteine for the patients who are vitamin B12 deficient?
A. It shows that the patients that had vitamin B12 deficiency had higher serum total homocysteine concentrations than normal subjects.
Q. And what does this paper show about patients who had a folate deficiency?
A. It shows that patients with folate deficiency had higher homocysteine levels than normal subjects.
Q. And why is homocysteine useful for determining both a folate and a B12 deficiency?
A. Homocysteine is useful as a marker for both folate and B12 deficiency because the metabolism of homocysteine requires both folate and B12.

Q. Were there techniques available as of June 1999 to measure levels of homocysteine in patients?
A. Yes. These techniques were pioneered by Dr. Allen and colleagues at the University of Colorado.
Q. And were there assays that were readily available to a person of ordinary skill in the art to use to measure homocysteine levels?
A. Yes.
Q. So what would a person of ordinary skill in the art have understood as of June 1999 from the fact that there was both, on the one hand, a correlation between elevated homocysteine and toxicity of pemetrexed and the fact that there was also an association between elevated homocysteine and folate and vitamin B12 deficiencies?
A. A person of ordinary skill in the art would have understood that a folate and/or B12 deficiency was associated with the toxicity of pemetrexed.
Q. Were there prior art references as of June 1999 that put those two things together and made the point that you just made?
A. Yes.
Q. Let's look at Trial Exhibit 2059.
And I would point you to page -- I think it's -- well, I'm going to point you to Abstract No. 62. And can you explain to the Court what this exhibit is?

A. Yes. This is an abstract from another European meeting called the ECCO, E-C-C-O, European cancer conference that was held in Hamburg, Germany, in September 1977, and the specific abstract, Abstract 62, is an abstract relating a folate status to the toxicity of pemetrexed, and is authored jointly by Lilly authors and the same Dr. Allen we've been just discussing.

Q. And what does it mean when it says -- in the same line where it gives the Abstract No. 62, it also says "poster." What does that mean?

A. Poster -- okay. As I explained previously, an abstract is essentially a request to present something or an application to present. And so the abstract is reviewed and considered by a committee of scientists as to whether it's of interest to be presented at the meeting, and so this was deemed to be of sufficient interest to be presented at the meeting. And so a poster presentation is -- means that you get a board that's, oh, it's probably about six feet by four feet to basically put your data on, and so you wouldn't just put the abstract on the board; you would put all of the data that supports the conclusions here in the abstract.

Q. And what study is this Zervos abstract in this Trial Exhibit 59? What study is it reporting the data from?

A. It's studies of -- in patients receiving pemetrexed in Phase 2 trials. It's basically the predecessor to the

Niyikiza abstracts.

Q. And what does this Zervos abstract say about the implications of the correlation between homocysteine and toxicity in that first paragraph?

A. Well, what it says is, first of all, that "studies in animal models and humans have revealed that folate nutritional status may be correlated with toxicity and antitumor activity of antifolates." So that's the first sentence. That's not referring to the data in this abstract. That's basically saying we knew this before we did the study.

And then the second sentence says, "Supplemental folic acid may play a role in protecting against the toxicities associated with antifolate drugs." Again, that's not based on the data in this abstract. They're saying, "We knew this. This is why we did this study." So, in a sense, these two sentences reflect what a person of ordinary skill in the art knew in 1997.

Q. Okay. And were there any other prior art references that they made this connection between folate status and toxicity of pemetrexed?

A. Yes.

Q. Let's turn to Trial Exhibit 1151. And if you could just remind the Court what this exhibit is.

A. This is Dr. O'Dwyer's paper again.

Q. And focusing on page 103 of this O'Dwyer paper, what does

Dr. O'Dwyer say about folate status?
A. Well, the last two sentences of the paper read as follows: "Work by Zervos, et al.," citing the exact same abstract we just looked at, "supports the position that toxicity may be increased in patients with poor nutritional status." And then not shown on the slide is the next sentence: "Additional studies are underway to explore the relationship between folate status and toxicity."
Q. Okay. And if you turn back one page to page 103, what else does Dr. O'Dwyer say about folate status and pemetrexed toxicity?
A. Well, Dr. O'Dwyer also references Niyikiza's work by stating, "The toxicity seen in this study" -- referring to a study in head-and-neck cancer patients, "The toxicity seen in this study is possibly related to nutritional status in this patient population. This hypothesis is supported by the work of Niyikiza, et al., who have shown that functional folate status is highly correlated to the instance of hematologic toxicity patients who received pemetrexed," and then it's reference 14, which is the Niyikiza 1998 ASCO abstract.
Q. Okay. Let's go on and talk about the final category of information that you said would have been available as part of the state of the prior art as of June 1999, and that's that vitamin B12 had been used with antifolates. When -- which -- for which antifolates had B12, vitamin B12 been used?

A. Vitamin B12 had been used with aminopterin and methotrexate.
Q. Okay. We've talked a little bit about aminopterin, but can you describe in more detail the use of vitamin B12 with aminopterin?
A. Aminopterin was the first antifolate that was administered to children and reported in 1948 by Sidney Farber, and Dr. Farber used liver extract to try and reduce the toxicity in these children. And a person of ordinary skill in the art in June of 1999 would be well aware that liver extract was an important source of vitamin B12.
Q. Let's take a look at that Farber exhibit again.
If you could turn to page 789, and let's look at Figure 2 as an example.
A. So I'm looking at page 789 of Exhibit 1443, and Figure 2 is a graph depicting the course of therapy in one particular patient.
Q. And what does Figure 2 report as the treatment that was given to that patient?
A. The chemotherapy treatment was aminopterin.
Q. And what else was administered to the patient?
A. The patient also received crude liver extract.
Q. Now, would a person of ordinary skill in the art as of June 1999 have known what the active component of crude liver extract was?

A. Yes.
Q. And how would that person have known that?
A. Well, it was described shortly after Dr. Farber's paper that crude liver extract contained vitamin B12, and this was explicitly called out in a 1975 paper by Halperin published in the proceedings of the National Academy of Sciences.
Q. Okay. Could you turn in your binder to Trial Exhibit 1336? Is this that Halperin paper that you were just referring to a moment ago?
A. Yes.
Q. Could you turn to page 4022, please? And what does Dr. Halperin say in this paper about the crude liver extract that was given in the study that's reported in the Farber paper?
A. Well, in this paper there was -- really focused on antifolates combined with folates. He notes, "Finally, it is only fitting to recall that in 1948 Dr. Sidney Farber treated children with acute leukemia with aminopterin as well as with injections of crude liver extract. The crude liver extract may well supply these very ill patients not only with vitamin B12 but also with an undetermined dose," and this is a folate, N5 methyltetrahydrofolate. And this is the concluding paragraph of this paper.
Q. Okay. Now, you also mentioned that vitamin B12 had been used with methotrexate. Can you describe that in more detail?

A. Yes. Dr. Morgan was very explicit in her work to measure baseline vitamin B12 prior to administration of folate and to replete vitamin B12 if patients were deficient. And so she administered methotrexate with folic acid with B12.
Q. Okay. Could you turn in your binder to Trial Exhibit 1204, please? Can you explain what this exhibit is?
A. This is a paper I alluded to earlier that was published in the *Annals of Internal Medicine*, which is the journal of the American College of Physicians. The society then encompasses all individuals certified in internal medicine.
Q. And what does Dr. Morgan report in this paper?
A. What Dr. Morgan reported here was a prospective randomized placebo controlled trial evaluating whether folic acid supplementation would reduce the toxicity of methotrexate in patients with rheumatoid arthritis.
Q. Now, if you turn to page 834 or Bates Number 696, under laboratory assessments, what does Dr. Morgan say in this article about vitamin B12?
A. What Dr. Morgan says is that at baseline all patients had their vitamin B12 measured.
Q. And what does the article say was the protocol if a patient had an abnormal level of vitamin B12?
A. What the paper says, if the patient had abnormal values for any of the vitamins, and this is vitamin B12 and others, other than folate, the abnormality was treated with single

vitamin supplements. So, if a patient had B12 deficiency, they would receive B12 supplementation.

Q. So, we've talked about aminopterin and methotrexate and their use with vitamin B12 in the prior art. Was there any suggestion about the use of vitamin B12 with pemetrexed in the prior art?

A. Well, yes. In other publications that were discussing the importance of nutrition in conjunction with pemetrexed, the point was made that both folate and B12 were potentially important.

Q. Okay. Let's take a look at one of those articles, if we could turn to Trial Exhibit 401, please.

And this is a exhibit we looked at before, but if you could just remind the Court what this exhibit is.

A. As a reminder, this is the first paper in the Ixtapa issue.

Q. And who is the author of this?

A. This is by Hilary Calvert.

Q. And okay. And what does -- looking at pages 8 and 9 of this paper by Dr. Calvert, what does Dr. Calvert say about vitamin B12 and pemetrexed?

A. Well, what Dr. Calvert says -- and first let me put this in context. This is a article on overview of folate metabolism in the context of a whole issue on pemetrexed.

Within that article, there's a section on clinical

measurement of functional folate status; and then he says, "Thus, any functional deficiency, either in B12 or folate, will result in reduction in the flux through methionine synthase and a consequent increase in the plasma level of homocysteine," and then refers to figure 8. And then Figure 8 very explicitly calls out that either folate or B12 deficiency affects the metabolism of homocysteine.

Q. And what does Dr. Calvert say in the very next sentence?

A. In the very next sentence, he says, "The measurement of pretreatment plasma homocysteine has proved to be a sensitive way of predicting the toxicity of pemetrexed."

Q. So what would a person of ordinary skill in the art then understand from this paragraph in this figure in Dr. Calvert's 1999 paper?

A. Well, one would read the sentence and one would see that the measurement of pretreatment plasma homocysteine is important in predicting the toxicity of pemetrexed; and then a person of ordinary skill in the art would then look at Figure 8 and see homocysteine, and then would see that either folate or B12 deficiency would be important considerations in evaluating a pretreatment plasma homocysteine.

Q. So what would a person of ordinary skill in the art be motivated to do with respect to vitamin B12 based on this suggestion in Dr. Calvert's article?

A. In looking at Dr. Calvert's article, a person of ordinary

skill in the art would be motivated to provide both folic acid and B12 supplementation pretreatment prior to pemetrexed.

Q. Is there any other prior art literature that makes a similar suggestion with respect to the addition of vitamin B12?

A. Yes. There's also a book chapter by Lilly authors.

Q. And is that the same book chapter we looked at earlier?

A. Yes, it is.

Q. I would like to just quickly take a look at that again. If you could turn to Trial Exhibit 400 in your binder.

And can you just remind us again what this book chapter is generally about?

A. Exhibit 400 is a book chapter generally about two GARFT inhibitors, lometrexol and the '887 compound.

Q. And if you could turn to page 270, there's a section entitled "Human Folate Status." Do you see that?

A. I see that.

Q. What's this section generally about?

A. This section is generally about the relationship of folate status in cancer patients to the toxicity of these two GARFT inhibitors.

Q. And what does Mendelsohn say in this chapter that's relevant about vitamin B12?

A. What Mendelsohn and colleagues state is, "The biochemical pathways that utilized folate cofactors also require adequate

amounts of vitamins B12 and B6. Thus, the status of all three vitamins in patients may significantly influence the severity of toxicity observed during chemotherapy."

Q. So what would a person of skill in the art again understand from the combination of both Mendelsohn and Calvert I with respect to vitamin B12?

A. A person of ordinary skill in the art would understand that B12 deficiency would be a risk factor for pemetrexed toxicity and similar antifolates.

Q. And what would the person of ordinary skill in the art then be motivated to do based on that information?

A. A person of ordinary skill in the art would be motivated to add B12, provide B12 supplementation prior to chemotherapy in addition to folic acid supplementation.

Q. Okay. Now that we've talked about the state of the prior art as of June 1999, I want to turn to talking about the specific opinions that you have rendered in this case. And let's start with your opinions about the obviousness of the -- of Claims 9 and 10.

Did you compare Claims 9 and 10 -- or the asserted claims generally to the prior art in this case?

A. Yes, I did.

Q. Which prior art did you compare it to?

A. I compared the asserted claims to Worzalla and also to the two Hammond abstracts.

Q. Okay. Actually, before we get to those asserted claims, you testified earlier that Claims 9 and 10 are dependent on Claim 1. So, why don't we start with Claim 1 which you said you had analyzed as well. Did you compare Claim 1 to the prior art?
A. Yes, I did.
Q. Which prior art was that?
A. The same prior art I just mentioned.
Q. Okay. So let's start with Worzalla. That was Trial Exhibit 384. Can you quickly remind the Court what Trial Exhibit 384, the Worzalla reference, was about?
A. Yes. The Trial Exhibit 384 is an article by Lilly authors, including the '974 inventor, evaluating the use of folic acid supplementation in mice. It's the article where we spent a lot of time on the graphs.
Q. And what are the differences between the Worzalla I reference, this Trial Exhibit 384 and Claim 1 of the '209 patent?
A. Well, the Worzalla paper did not utilize B12; and second of all, of course, the Worzalla paper reports a study in an animal model cancer, not in patients with cancer.
Q. Okay. You said that you also compared Claim 1 to the Hammond abstracts. I know we just talked about it, but can you quickly remind the Court what the Hammond abstracts were about?

A. The Hammond abstracts were regarding a Phase 1 trial of pemetrexed with folic acid pretreatment.
Q. And what were the differences between the Hammond abstracts and Claim 1 of the '209 patent?
A. The difference between the Hammond abstracts and Claim 1 of the '209 patent is that the Hammond abstracts did not utilize vitamin B12.
Q. So, let's start with the Hammond abstracts. Would a person of ordinary skill in the art have been motivated to modify the Hammond abstracts?
A. Yes.
Q. What modifications would the person of ordinary skill in the art have been motivated to make to those abstracts, a regimen in those abstracts?
A. A person of ordinary skill in the art would have been motivated to add B12 pretreatment.
Q. And then the same question, starting with the Worzalla I paper. Would the person of ordinary skill in the art have been motivated to modify what's disclosed in Worzalla I?
A. Yes.
Q. And how -- what modifications would the person of ordinary skill in the art have made to the treatment regimen set forth in the Worzalla I paper?
A. Well, the most obvious modification is to apply the principles taught by Worzalla to the treatment of patients

with cancer. And then, in addition, to administer vitamin B12.

Q. Okay. So in both instances, for Worzalla and for the Hammond papers, you said a person of ordinary skill in the art would have been motivated to add vitamin B12. Why would the person of ordinary skill in the art have been motivated to add vitamin B12?

A. Well, it all comes back to the thought processes here; and so a person of ordinary skill in the art who's motivated to try and reduce the toxicity of an antifol that is believed to be due to a nutritional deficiency would understand that to effectively do so, one would potentially need to include both folic acid and B12 as supplementation.

Q. And can you just -- okay. And is there any other reason why a person of ordinary skill in the art would have been motivated to add vitamin B12 pretreatment to both Worzalla and the Hammond papers?

A. Well, in addition, there would also be a concern about giving folic acid alone, as the literature suggests, that vitamin B12 should be given with folic acid pretreatment to avoid hidden complications of vitamin B12 deficiency.

Q. Okay. We're going to focus largely on that first reason you talked about with respect to pemetrexed-related toxicity, but can you very briefly just describe in a little bit more detail what you meant by avoiding hidden complications of a

vitamin B12 deficiency?
A. Well, this -- there are potential problems if one treats a patient who has a B12 deficiency with folic acid alone. And this is just basic medicine that we're all taught, that if you suspect a deficiency of either folic acid or B12, you need to make sure that you make the right diagnosis, because if you just treat with folic acid when the patient has B12 deficiency, the patient will develop neurologic complications, in theory. I agree this is a theoretical concern, but it's a theoretical concern that is very serious and irreversible.
Q. Okay. We're going to hear more about that from other experts in the case, so for the moment I want to focus on the other reasons that you mentioned. The literature suggested that vitamin B12 could reduce pemetrexed toxicity. Can you provide more detail about what literature you're referring to when you say that the literature suggested that vitamin B12 could reduce pemetrexed toxicity?
A. Well, the logic is as follows: We've discussed that there's evidence of an association or correlation between homocysteine levels prior to chemotherapy and the instance and severity of pemetrexed toxicity. We've discussed that there's evidence of an association between folate and/or B12 deficiency and an increase in homocysteine levels.
And therefore, a person of ordinary skill in the art would understand that folate and/or B12 deficiency could be

contributing to severe pemetrexed toxicity; and furthermore, that's explicitly discussed in several prior art references.
Q. So what would the person of ordinary skill in the art then do, starting from Worzalla I or the Hammond abstracts, in view of these teachings in the prior art that we've discussed?
A. A person of ordinary skill in the art would add vitamin B12.
Q. And with respect to Worzalla, what would the person of ordinary skill in the art do with respect to the treatment group?
A. A person of ordinary skill in the art would apply the principles taught in Worzalla to the treatment of patients.
Q. And this may sound like a silly question, but what would be the motivation to move from the mice to treating patients?
A. Well, a person of ordinary skill in the art we have defined as physicians here, and so physicians are interested in helping patients with cancer, and, therefore, would be readily motivated to treat patients rather than doing more experiments in the laboratory.
Q. Okay. And on the topic of the person of ordinary skill in the art, are you aware that the Court has rendered an opinion -- a preliminary opinion in this case the qualifications of the person of ordinary skill in the art?
A. Yes.
Q. And the Court's opinion was that the person of ordinary

skill in the art can be a medical doctor who specializes in oncology or a medical doctor with extensive experience in the areas of nutritional sciences involving vitamin deficiency. However, as to the latter person, this individual would need to have collaborated with medical oncologists who have knowledge and experience -- sorry.

THE COURT: And, Counsel, do you have an objection?

MR. PERLMAN: I guess my objection is it doesn't sound like there's a question in our future.

MS. RAPALINO: I'm getting there.

THE COURT: If you would just slow down for the court reporter.

MS. RAPALINO: Sure. I'm sorry about that.

Can I start with "however"?

BY MS. RAPALINO:

Q. However, as to the latter person, this individual would need to have collaborated with medical oncologists who have knowledge and experience in the treatment of cancer through the use of antifolates.

If the Court were to adopt that definition of a person of ordinary skill in the art, would that change your opinions in any way in this case?

A. No.

Q. Okay. Now, you just testified that a person of ordinary skill in the art, starting with Worzalla or Hammond, would be

motivated to add vitamin B12 pretreatment. Would the person of ordinary skill in the art necessarily supplement all patients with vitamin B12?

A. One, a person of ordinary skill in the art could either supplement all patients with B12 or alternatively, evaluate for the possibility of B12 deficiency using routine diagnostic tests known at the time, and then treat only the B12-deficient patients with B12.

Q. And would the person of ordinary skill in the art have had motivation to treat vitamin B12-deficient patients with vitamin B12 prior to pemetrexed?

A. Yes. A person of ordinary skill in the art would be motivated to treat B12 deficiency with B12 prior to pemetrexed.

Q. So before we move on to the dependent claims in this case, can you just summarize why the method of Claim 1 of the '209 patent would have been obvious to a person of ordinary skill in the art?

A. Well, it's summarized here. A person of ordinary skill in the art would start with these contemporary prior art references from really 1998 and would understand that there's evidence that folic acid pretreatment was -- would reduce the toxicity of pemetrexed and maintain the therapeutic activity.

And therefore, a person of ordinary skill in the art would add vitamin B12 pretreatment to reduce the homocysteine

levels known to be correlated with pemetrexed toxicity, as well as to prevent the potential complications of a hidden vitamin B12 deficiency.

Q. Okay. Let's turn to the asserted claims in this case, starting with Claim 9. And if you could turn to Trial Exhibit 1 in your binder.

What additional limitations does Claim 9 add to the limitations that are already in Claim 1 of the '209 patent?

A. Claim 9 adds the limitation of the folic acid dose from about 350 micrograms to about 1,000 micrograms.

Q. And looking at Claim 10, also in Column 11 of Trial Exhibit 1, what additional limitation does Claim 10 add to Claim 1 of the '209 patent?

A. Claim 10 further narrows the folic acid dose to -- from -- to 350 micrograms to 600 micrograms.

Q. Does the additional limitation of a dose range of either 350 micrograms to 600 micrograms or 350 micrograms to 1,000 micrograms of folic acid render these claims non-obvious?

A. No.

Q. Why not?

A. Because these are standard, routine doses of folic acid included in standard, over-the-counter, readily available multivitamin supplements.

Q. And would this have been well-known to a person of ordinary skill in the art as of June 1999?

MR. PERLMAN: Objection.

THE COURT: Leading.

BY MS. RAPALINO:

Q. What would a person of ordinary skill in the art have known about doses of folic acid as of June 1999?

A. A person of ordinary skill in the art would know that these are standard doses of folic acid supplementation.

Q. Dr. Ratain, don't the Hammond abstracts upon which your obviousness positions depend use a 5-milligram dose of folic acid?

A. Yes.

Q. So, why would a person of ordinary skill in the art modify the dose of folic acid that was used in the Hammond abstracts, the 5-milligram dose, to arrive at the claimed doses?

A. Well, there are two basic reasons why one would want to modify the folic acid dose in Hammond. One relates to convenience, and the other relates to theory.

Q. Okay. Let's start with the first one, with convenience. Can you explain what you mean by that?

A. Well, 5 milligrams of folic acid is a prescription dose folic acid that's not always available, particularly in the context of a potential international study.

Q. And so what would that mean in terms of the motivation of a person of ordinary skill in the art?

A. A person of ordinary skill in the art, understanding that

the goal here is to just give enough folic acid to treat some mild folic acid deficiency, would understand that all they need to do is give enough folic acid that's contained in multivitamins, and, therefore, could just use that lower dose of folic acid than the stronger prescription dose.

Q. And what was the other reason you mentioned, the one that relates to theory for why a person of ordinary skill in the art would modify the dose of Hammond?

A. Well, there's always the theoretical concern that folic acid can reduce the efficacy of antifolates. And clearly, at very high doses, that's going to be a concern; and at very low doses, it wouldn't be a concern.

And it's not clear exactly what the optimal dose is; but therefore, one would be motivated to go down on the dose and use a dose that achieves the goal that one is trying to accomplish. In this case, the goal is to simply normalize the folate pools, normalize the folate stores, and provide these physiologic replacement doses of folic acid rather than a higher pharmacologic dose of 5 milligrams.

Q. And what doses of folic acid are physiologic doses of folic acid?

A. These are doses in the range of 350 to 1,000 micrograms.

Q. Okay. Let's turn to Claim 12 of the '209 patent. What limitations does Claim 12 set forth that are not present, for example, in Claim 1 of the '209 patent?

A. Well, if one compares Claim 12 to Claim 1, there's a limitation on the folic acid dose. There's a limitation on the vitamin B12 dose.
Q. And what's the limitation on the folic acid dose in Claim 12?
A. The limitation of the folic acid dose is that it's the same limitation as in Claim 9, 350 to 1,000 micrograms of folic acid.
Q. And what's the limitation on the vitamin B12 dose in Claim 12?
A. The limitation of the vitamin B12 dose is from about 500 micrograms to about 1,500 micrograms of vitamin B12.
Q. Let's look at the next asserted claim, and that's Claim 14. What additional limitations does that claim add?
A. Claim 14 adds the additional limitation of an intramuscular injection of vitamin B12.
Q. And then moving on to Claim 18 of the '209 patent, what additional limitation does claim -- I'm sorry. I skipped Claim 15.

What additional limitation does Claim 15 of the '209 patent add?
A. Well, Claim 15 limits the dose of vitamin B12 to exactly about 1,000 micrograms.
Q. And does it have any limitation on the route of administration?

A. Yes. It's the same limitation as in Claim 14 of an intramuscular injection.
Q. And then moving on to Claim 18, what additional limitations does Claim 18 add?
A. Claim 18 further limits the folic acid dose to the same as in Claim 10, 350 micrograms to 600 micrograms.
Q. Do any of the limitations on the dose of vitamin B12 render these claims non-obvious?
A. No.
Q. Why not?
A. These are all routine, standard, everyday doses of folic acid and B12.
Q. And what would a person of ordinary skill in the art have known about the doses of vitamin B12 as of June 1999?
A. A person of ordinary skill in the art would have known that these doses are just within the range of standard routine doses.
THE COURT: When you say "standard routine doses," you mean like if I just went to the drugstore and wanted to take B12?
THE WITNESS: No. These are standard B12 doses for treating B12 deficiency.
THE COURT: Standard as opposed to what? As opposed to if your doctor gives you a prescription or --
THE WITNESS: Yes. These doses, if a physician

wanted to treat a patient for a B12 deficiency, this is how the patient would be treated. This would be one option, to treat with a dose of about 1,000 micrograms given as an intramuscular injection.

THE COURT: Okay. Thank you.

BY MS. RAPALINO:

Q. And I think you just said this, but was the route of administration of vitamin B12, does that render these claims non-obvious?

A. Not at all, because an important cause of vitamin B12 deficiency is the fact that there's a problem with the gastrointestinal tract.

Q. And so how does that implicate the route of administration of vitamin B12?

A. It would mean that giving vitamin B12 orally would run the risk of not being absorbed; and therefore, if one wanted to be certain that one was treating B12 deficiency, then one would want to give B12 as an intramuscular injection.

Q. And would a person of ordinary skill in the art have been aware of common routes of administration of vitamin B12 as of June 1999?

A. Yes.

Q. Does the '209 patent specification itself say anything about what was known in the prior art with respect to the dose of vitamin B12?

A. Yes, it does.
Q. Okay. Let's look at Column 5 of the '209 patent. And starting around line 19 of Column 5, what does the '209 patent say was known in the prior art about the dose of vitamin B12?
A. It states that, "The skilled artisan will appreciate that the methylmalonic-lowering agents are effective over a wide dose range."

And then it goes on to say, for example, when cobalamin is used as the methylmalonic-lowering agent, the dosage of cobalamin may fall within the range from about 0.2 micrograms to about 3,000 micrograms.

What it's telling you is that you have a 15,000-fold dose range that would be acceptable for cobalamin, which is not the B12 we're talking about, but is -- was an alternative considered in the -- by the original inventors.
Q. What does the '209 patent say in that same column about adjustments to dose of vitamin B12?
A. In the same column, it adds, "However, it will be understood that the amount of the methylmalonic acid-lowering agent actually administered will be determined by a physician in light of the relevant circumstances, including the condition to be treated, the chosen route of administration, the actual agent administered, the age, weight and response of the individual patient, and the severity of the patient's

symptoms. Therefore, the above dosage ranges are not intended to limit the scope of the invention in any way."

Q. And so what does the '209 patent say about what was known in the prior art about doses of vitamin B12?

A. Well, the '209 patent basically says there's a whole range of doses. It doesn't really matter that much what the dose is, and the physician should just use routine medical judgment.

Q. Does the '209 patent say anything about the route of administration of vitamin B12 -- I'm sorry -- what was known in the prior art about the route of administration of vitamin B12?

A. Yes. The patent, the same column, Column 5, specifically says that, "Preferably, the methylmalonic acid-lowering agent is administered as intramuscular injection formulation. Such formulations are known in the art and are commercially available."

Q. Okay. Now that we've looked at those dose and route of administration limitations in Claims 12, 14, 15 and 18, let's turn to the last of the asserted claims, Claims 19 and 21.

What limitation does Claim 19 add that we haven't already talked about?

A. Claim 19 of the '209 patent adds the limitation of the time interval between folic acid initiation and pemetrexed initiation.

Q. And what is the time interval specified in Claim 19?
A. The time interval is one to three weeks.
Q. And so does the limitation in the time interval of one to three weeks between folic acid administration and the first administration of pemetrexed render Claim 19 non-obvious?
A. No.
Q. Why not?
A. Again, the purpose of giving the folic acid is to normalize the potential deficiency of folate in the patient; and, therefore, what one would want to do, especially since one -- if one is motivated to give a low dose, is to start that dose early enough so that the folate can build up over time.
Q. And what would a person of ordinary skill in the art have known about the schedule for folic acid that would allow the dose to build up over time?
A. Well, a person of ordinary skill in the art would know this had been used previously.
Q. And what would they know about that? Are you referring to specific literature?
A. Yes.
Q. And what literature are you referring to?
A. It's -- there's a discussion of this in two prior art references, basically describing prior trials by Lilly with

the GARFT inhibitor, two different GARFT inhibitors where the folic acid was begun a week before the chemotherapy.

Q. Okay. Generally speaking, as of June 1999, what was the route of administration generally for folic acid?

A. Folic acid was generally given orally.

Q. And would the route of administration for folic acid have been known to a person of ordinary skill in the art as of June 1999?

A. Yes.

Q. So you mentioned that there were two prior art references that talked about a schedule of folic acid pretreatment. Let's look at one of those, at Trial Exhibit 400.

And actually, I'm sorry. Let's start with Trial Exhibit 1036, if we could.

This is the Laohavinij article that we talked about earlier?

A. Yes.

Q. And what does this study -- what would this study teach a person of ordinary skill in the art about the schedule of folic acid pretreatment with an antifolate?

A. Well, the investigators in this study utilized folic acid given daily beginning seven days prior to the chemotherapy. The chemotherapy was lometrexol, another Lilly antifolate.

Q. And so what would that teach a person of ordinary skill in the art about an appropriate schedule of folic acid

pretreatment?
A. This would -- this study would teach a person of ordinary skill in the art to start the folic acid supplementation a week before the chemotherapy.
Q. And if we could turn to Trial Exhibit 400 now. This is that book chapter from Mendelsohn we looked at earlier. What would this teach a person of ordinary skill in the art about the schedule of folic acid pretreatment?
A. This paper -- and I'm trying to find the page -- but it basically noted that the '887 compound was tested in Phase 1 studies with folic acid supplementation, using the same schedule as with the lometrexol compound, beginning a week prior to the chemotherapy.
Q. And if you could turn to page 277 of this chapter and the first full paragraph, is that -- is that the part of this paper you're referring to?
A. Yes. There's a sentence, "The latter schedule is, therefore, identical to that used in the lometrexol study performed by Laohavinij, et al.," and it's referring to a study of folic acid with the '887 compound.
Q. Okay. So what would a prior -- what would a person of ordinary skill in the art then have understood from this prior art literature and from their general knowledge about an appropriate dose of folic acid or appropriate timing of folic acid administration prior to pemetrexed?

A. A person of ordinary skill in the art would understand that it was reasonable and appropriate to begin folic acid supplementation a week or even more than a week before starting chemotherapy.

Q. Okay. Let's turn back to Trial Exhibit 1 and look at the last claim of the '209 patent. The last asserted claim, rather, Claim 21.

What additional limitations does Claim 21 add that we haven't already discussed with respect to the other asserted claims?

A. Claim 21 of the '209 patent adds the limitation of repeating the intramuscular injection of the vitamin B12 about every six to about every 12 weeks.

Q. And does that schedule of administration of vitamin B12 render Claim 21 non-obvious?

A. No.

Q. Why not?

A. Well, because, one, if one is motivated to give vitamin B12, one would know that one needs to give more than a single injection, and one would want to repeat the vitamin B12 at some periodic intervals. And the patients are given the chemotherapy every three weeks, so it's perfectly reasonable to repeat the injection every six weeks, every nine weeks or every 12 weeks. That's just a routine medical practice.

Q. Would the person of ordinary skill in the art have been

aware of this routine medical practice as of June 1999?
A. Yes.
Q. Now, you mentioned that you also had an opinion regarding the reasonable expectation of the person of ordinary skill in the art. What conclusion did you reach regarding what reasonable expectation a person of ordinary skill in the art would have had with respect to pemetrexed with folic acid and vitamin B12 pretreatment at the claimed doses and schedules?
A. The person of ordinary skill in the art would have reasonably expected that folic acid and vitamin B12 pretreatment with pemetrexed would provide a therapeutic benefit at the claimed dose and schedule.
Q. And what is that opinion based on?
A. It's based on everything we've discussed.
Q. Can you be a little more specific?
A. Sure. Well, first of all, there was a reasonable expectation that folic acid pretreatment would reduce toxicity and maintain efficacy. And we've gone through many prior art references on this topic. And then there would be a reasonable expectation that an addition of vitamin B12 would not impact efficacy.
Q. And what's the basis for your -- for your opinion that the addition of vitamin B12 would not impact the efficacy of pemetrexed with folic acid pretreatment?
A. Well, oncologists give vitamin B12 to cancer patients all

the time. We are constantly telling patients to keep up their nutrition. We're constantly providing nutritional supplements, both little cans of nutritional supplements that contain B12, some patients get two tube feedings, some patients get total parental nutrition, which is basically intravenous feeding. All of these nutritional approaches include vitamin B12, and one would never be concerned about the possibility of the vitamin B12 stimulating the tumor growth.

Q. Aren't there references that suggest that vitamin B12 could promote tumor growth?

A. Yes. I've seen them, but only in the context of this litigation.

Q. And why wouldn't those references undermine the reasonable expectation of success of a person of ordinary skill in the art in adding vitamin B12 when treating a patient with cancer?

A. Well, the -- there's clear evidence that from just clinical experience that adding vitamin -- administering vitamin B12 to patients is not harmful. There's also no teaching in any medical textbooks or any U.S. labels for vitamin B12 that suggests any contraindication for administration of vitamin B12 in cancer patients.

Q. Have you reviewed any labels for vitamin B12 to see whether there were any such contraindications?

A. Yes, I have.

Q. Could you look at Trial Exhibit 1374 in your binder?
Can you explain what this trial exhibit is?
A. This is a portion of the 1999 Edition of the *Physicians' Desk Reference*.
Q. And what is the *Physicians' Desk Reference*?
A. The *Physicians' Desk Reference* is a privately published compendia of FDA-approved labels for drugs and anything that FDA regulates, any drug products.
Q. And if you look at page Bates No. 2917, what is this excerpt of the *Physicians' Desk Reference* about?
A. Page 2917 of this exhibit is the package insert for a vitamin B12 supplement called Nascobal.
Q. And have you reviewed the contraindications section of this label?
A. Yes, I have.
Q. Have you reviewed the warning section of this label?
A. Yes, I have.
Q. Have you reviewed the precautions section of this label?
A. Yes, I have.
Q. And do any of those sections contain any warning, precaution, suggestion, contraindication that vitamin B12 should not be used in a cancer patient?
A. No.
Q. Have you reviewed the entire -- the entirety of this label for the vitamin B12 supplement?

A. Yes, I have.
Q. And is there any suggestion in there that vitamin B12 shouldn't be used in cancer?
A. No.
Q. Was there any of the literature that you reviewed with respect to antifolates that supports your opinion that there would have been no concern about impacting the efficacy of an antifolate, much less stimulating tumor growth, when you're giving antifolate with vitamin B12?
A. Well, we also have the first antifolate administration by Farber in 1948, as well as papers that have cited that, and nobody has ever suggested that Dr. Farber did anything wrong by administering crude liver extract to these children with leukemia.
Q. Is there any other -- have you seen any other -- have you reviewed any other documents that suggest that there was no concern in the literature about vitamin B12 stimulating tumor growth?
MR. PERLMAN: Objection. If I'm jumping ahead on the slide, it appears the answer is going to be another one of these postdated FDA documents that Lilly submitted, and I object for the same reasons as previously stated.
MS. RAPALINO: I think this is a different issues, Your Honor. This is a party admission about what -- factually about what was or wasn't available in the literature.

MR. PERLMAN: Your Honor, that admission is in the document. It's there in evidence, and it can be used for whatever it's used for, but it has no bearing on what the person of ordinary skill would have known or thought in June 1999, and Dr. Ratain is not an expert in opining on what search Lilly did or what the fact they couldn't find something that we all know today exists means to this case. It's not as if there isn't something. All this proves is whoever did the search in 2000 didn't find it, which doesn't bear on any issue in this case.

MS. RAPALINO: And I think that's a proper subject for cross-examination or for Lilly's experts to testify about, but to the extent Dr. Ratain is aware of evidence that there -- of what was or wasn't available in the literature, factually speaking, as of 2000 --

THE COURT: 2000.

MS. RAPALINO: -- which, again, is just cumulative of what wasn't -- things that were variable as of 2000 -- I'm sorry -- things that weren't available as of 2000 would not have been available as of 1999, as well.

MR. PERLMAN: Your Honor, he can testify as to what the person of ordinary skill would have known or not known, but the fact that a year later Lilly said, "Somebody did a search and we didn't find it," doesn't bear on the question of what the person of ordinary skill would have known. I'm not

saying this argument is an improper argument. It's an improper line of testimony for this witness.

THE COURT: What is your question for this witness --

MS. RAPALINO: I'm going --

THE COURT: -- with respect to this exhibit? What will your question be?

MS. RAPALINO: Okay. I'm going to have to turn to the exhibit just to take a look at it really quickly.

MR. WIESEN: May I approach?

THE COURT: You may consult with your co-counsel.

(Off the record.)

MS. RAPALINO: Your Honor, if Mr. Perlman is acknowledging that this document is in evidence, then we don't need Dr. Ratain to sponsor it or to offer it into evidence, but, again, if he's not, then I think we just need this witness to sponsor the exhibit and to offer it into evidence and to explain what it says --

MR. PERLMAN: Your Honor --

MS. RAPALINO: -- and what it is.

MR. PERLMAN: Your Honor, this is a Lilly submission to the FDA. It is admissible into evidence with the appropriate foundation. The fact that they showed it to their expert and he put it in his expert report doesn't move it into evidence. My statement that it is an admissible document, it

is an admissible document. They can admit it. We're not contesting what the document is. But what I am saying, is to have their expert get on the stand and basically be a parrot for their closing argument is not an appropriate use of the expert.

MS. RAPALINO: Right. And I think that part of what I want to do is set a foundation with Dr. Ratain for what this document is. He has experience dealing with FDA, and he can explain what the document is so that we can offer it into evidence. And then to the extent that any characterization he makes of the document is inadmissible, that would be -- that's okay. We're just trying to get this document into evidence.

MR. PERLMAN: Your Honor, he doesn't have any personal knowledge of this document. But if the issue is, can they get this document admitted into evidence, that's not going to be an issue at this trial.

MS. RAPALINO: He's not here as a fact witness; he's an expert witness. So the fact that he doesn't have personal knowledge isn't really relevant to his ability to testify about it and get it into evidence.

MR. PERLMAN: Of course, it is, Your Honor, because the last argument was, he can lay the foundation for what the document is. And so now we hear he's not a fact witness and so it doesn't matter if he doesn't know what the document is.

MS. RAPALINO: Right. No --

MR. PERLMAN: Pardon. Pardon me.

Your Honor, this issue is not about the document. This issue is about what is the appropriate use of a medical expert's testimony to make argument based on a document that is not part of the relevant prior art? That's the basis of my objection. This document is separately admissible through other witnesses, Lilly employees who were deposed in this case; they were deposed on this document. They have the deposition transcripts to authenticate and lay the foundation for this document. Dr. Ratain knows no more about this document than you and I do in terms of laying a foundation for its admissibility.

MS. RAPALINO: Okay. I'm just going to disagree. Dr. Ratain does have the expertise to look at this document and determine what it is and lay the foundation for it. And, you know, I feel like there are potentially many ways to get this document into evidence, but I feel like it's -- you know, part of presenting our case is our determining how we want to get the document into evidence.

THE COURT: And you're not going to ask him questions about the document?

MS. RAPALINO: To the extent that the Court finds those questions objectionable, I won't ask those questions about the document.

THE COURT: You just want to get it in now?

MS. RAPALINO: Yes.
MR. PERLMAN: Get it in. If they're not going to ask any questions about it, get it in.
THE COURT: All right. Go ahead and offer it. He probably won't object to you offering it.
MS. RAPALINO: Okay.
MR. PERLMAN: Okay. As long as we're not going to have testimony that I don't think is proper.
BY MS. RAPALINO:
Q. Dr. Ratain, could you take a look at Trial Exhibit 339 in your binder, please?
MR. PERLMAN: Your Honor, I will stipulate to the admissibility of 337 if it will save having to go through --
THE COURT: Okay.
MR. PERLMAN: -- this exercise, and so we can just move on.
THE COURT: Why don't we do that, and then we can move on. The parties stipulate to the admissibility of 337.
(Plaintiff's Exhibit 337 was received in evidence.)
MS. RAPALINO: Thank you, Your Honor.
THE COURT: Next question.
BY MS. RAPALINO:
Q. So, Dr. Ratain, just to sort of reorient us to where we were, can you just summarize the basis for your opinion that a

person of ordinary skill in the art would have a reasonable expectation that the addition of vitamin B12 would not impact the efficacy of pemetrexed?
A. Well, as I just discussed, there's abundant use of vitamin B12 by oncologists in patients with cancer and poor nutrition. Prior to this case, I have never, ever heard of a physician being concerned about the risk of giving vitamin B12 to a cancer patient. And so it just -- it's not a credible concern, in my mind, given my personal experience taking care of cancer patients, my review of the entirety of the prior art, and my review of FDA labels.
Q. Have you ever advised a patient with cancer not to take vitamin B12?
A. Absolutely not.
Q. Okay. And so now, just to summarize your opinions with respect to obviousness, can you please tell the Court your opinion regarding whether asserted Claims 9, 10, 12, 14, 15, 18, 19, and 21 of the '209 patent are obvious?
A. It's my opinion that all the asserted claims of the '209 patent are obvious.
MS. RAPALINO: Okay. I would like to switch topics now and start talking about our double patenting defense and elicit testimony from Dr. Ratain on that. Is this a -- should I proceed?
THE COURT: Sure. Go ahead.

MS. RAPALINO: Okay.
BY MS. RAPALINO:
Q. Okay. Let's talk about your opinions on double patenting now. You previously testified that you rendered opinions in this matter regarding whether the claims of the '209 patent are obvious variance of the '974 patent. Can you just reiterate your opinion on double patenting?
A. My opinion is that the asserted claims of the '209 patent are obvious variance of Claim 20 of the '974 patent.
Q. Okay. I want to again focus on the asserted claims, and I'm going to ask you whether you had a particular framework for your obviousness-type double patenting opinion?
A. Well, yes. The approach I used was to first consider the differences between the asserted claims and Claim 20 of the '974 patent and then to analyze whether those differences render the asserted claims obvious variance of Claim 20 of the '974 patent.
Q. Okay. Let's turn to the '974 patent, which is Exhibit 916 in your exhibit binder. And can you just remind the Court who owns this nine -- to whom is the '974 patent assigned?
A. Eli Lilly and Company.
Q. And to whom is the '209 patent that's at issue in this case assigned?
A. The same.

Q. Okay. Let's take a look at Claim 20 of the '209 patent. I'm sorry. Claim 20 of the '974 patent.

Does Claim 20 depend on any other claims?

A. Yes.

Q. From which claims does it depend?

A. Well, Claim 20 depends on -- depends from Claim 19, which depends from Claim 18, which depends from Claim 16.

Q. Okay. So, taking all the limitations of Claim 20 along with the claim limitations of the claims from which it depends, if you were to rewrite Claim 20 in independent form, what does Claim 20 cover?

A. Well, I've rewritten it in independent form as shown on this slide, and --

Q. By "this slide," you're referring to Slide -- let me see the number here. Is it 144?

THE COURT: Yes. 144.

MS. RAPALINO: Okay.

BY MS. RAPALINO:

Q. Go ahead, Dr. Ratain.

A. And when you do -- when you go through that exercise, you get the following: A method for reducing the toxicity of a GARFT inhibitor or other antifolate which binds to an FDP in a mammal which comprises pretreating the mammal with about 0.5 milligrams to about 30 milligrams of folic acid about one to 24 hours before administration of the antifolate.

Q. Now, does Claim 20 of the '974 patent that you just read and as rewritten in independent form, would that cover the approved use of pemetrexed with folic acid and vitamin B12?
A. Yes.
Q. And how do you know that?
A. Well, pemetrexed is -- inhibits GARFT. It also binds to FBP. Folic acid is administered earlier, and in addition, I've reviewed documents from the Eli Lilly to the FDA that basically has requested that FDA list the '974 patent in conjunction with the marketing approval of Alimta.
Q. Okay. Let's turn to Trial Exhibit 1386.
And is this that correspondence that you were just referring to?
A. Yes.
Q. Can you explain what this document is?
A. Yes. This document is a letter from Eli Lilly, John Worzalla, to the FDA Office of Generic Drugs, with a completed FDA Form 3542, which includes the information regarding the '974 patent.
Q. Okay. And can you turn in this exhibit to a page ending in Bates No. 44004? What patent is referenced in this form that Lilly submitted to the FDA?
A. Well, in this document, which I should add, this is a form entitled "Patent information submitted upon and after approval of an NDA or supplement." The specific patent that's listed

on this form is the same as the '974 patent.
Q. And if you turn to page 44007 -- sorry -- it's Bates No. 44007, and at the top of the page do you see that there's a box that says "patent claim number," and there's a "20"? What does Lilly say in the next box with respect to Claim 20 of the '974 patent?
A. Lilly stated that the Claim 20 of the '974 patent claims an improved method of use of Alimta.
Q. And if you look at the "use" box just under that on the same page, 44007, what use is indicated as being covered by Claim 20 of the '974 patent?
A. The form indicates that the use that's being covered is the premedication regimen, specifically the vitamin supplementation. "To reduce toxicity, patients treated with Alimta must be instructed to take a low dose oral folic acid preparation or multivitamin with folic acid on a daily basis."
Q. Okay. So what is Lilly telling the FDA here about the '974 patent and in particular Claim 20?
A. Lilly is telling the FDA that the '974 patent covers -- their use of Alimta covers the vitamin regimen incorporated into the label.
Q. Okay. I'd like you now to go to Trial Exhibit 916, which again is the '974 patent, and also, if you can, keep a finger in Trial Exhibit 1, which is the '209 patent-in-suit here. And focusing on the first two of the asserted claims of

the '209 patent, Claims 9 and 10, did you do a comparison of these claims to Claim 20 of the '974 patent?
A. Yes, I did.
Q. And have you prepared a chart to walk through that comparison?
A. Yes, I have.
Q. Okay. And if we look at Slide 147, is this the chart you prepared?
A. Yes.
Q. Okay. Can you explain with reference to this chart how Claims 9 and 10 of the '209 patent compare to Claim 20 of the '974 patent?
A. Well, there are a number of differences between Claims 9 and 10 of the '209 patent when rewritten in this independent form as compared to Claim 20 of the '974 patent. So, the first limitation is that the '209 patent limits the drug to pemetrexed; whereas, the '974 patent limits the drug to a GARFT inhibitor or other antifolate. And the '209 patent limits the administration to a patient in need thereof, and the '974 patent limits the administration to a mammal.
Q. Now, would a person of ordinary -- so is pemetrexed disodium a GARFT inhibitor?
A. Yes, it is.
Q. And is pemetrexed disodium an antifolate which binds to a folate binding protein?

A. Yes.
Q. Would a person of ordinary skill in the art as of June 1999 have had a reason to select pemetrexed or pemetrexed disodium as the drug of choice from amongst the GARFT inhibitors or other antifolates which bind to a folate binding protein?
A. Yes. It was certainly the most exciting GARFT inhibitor still in development at that time and clearly was probably the most exciting antifolate, period, in development at the time, as demonstrated by some of Dr. Calvert's comments about the remarkable and exceptional clinical activity observed.
Q. And you said that Claims 9 and 10 refer to a patient in need thereof, whereas Claim 20 of the '974 patent talks about a mammal. Would a person of ordinary skill in the art in June 1999 have had a reason to treat a patient from amongst the many possible mammals?
A. Yes, because a POSA, as defined in this case, is a physician who treats humans.
Q. Okay. Can we move on to the next limitation in your chart? And can you explain how those limitations in Claims 9 and 10 of the '209 patent compare to the limitation in Claim 20 of the '974 patent?
A. Well, the second limitation of the '209 patent relates to the dose of the folic acid, and it's in the range of 350 to 1,000 or 350 to 650 micrograms; whereas, the '974 patent has

different units, milligrams, but if we translate these units of milligrams into micrograms, it would be 500 micrograms to about 30,000 micrograms. So there's an overlap in the folic acid dose range between the Claims 9 and 10 of the '209 patent and Claim 20 of the '974 patent.

Q. And would a person of ordinary skill in the art have had a reason to select a dose range falling within the claims of the -- falling within the range of 350 to 1,000 micrograms or 350 to 650 micrograms of folic acid?

A. Yes. These are just obvious variance of the dose limitation in the '974 patent Claim 20.

Q. And I think there might be a typo on the slide, so I just want to point it out to you and ask whether that's the case. If you look at Claim 10 of the '209 patent, what range of folic acid is covered by Claim 10 of the '209 patent?

A. You are correct; it's my mistake. It's -- Claim 10 of the '209 patent is a range of 350 micrograms to 600 micrograms.

Q. And does that change your opinion regarding whether a person of ordinary skill in the art would have selected this dose?

A. No, it does not.

Q. Okay. And then can we move on to the next limitation in your chart comparing Claims 9 and 10 of the '209 patent to Claim 20 of the '974 patent?

A. Well, the next limitation of Claims 9 and 10 of the '209 patent is to add B12 to the regimen, and we've been talking about this earlier today.
Q. And would the addition of vitamin B12 -- well, could you tell us specifically what the limitations are in Claims 9 and 10 of the '209 patent with respect to vitamin B12?
A. Well, there's quite a range of options of the B12 dose in Claims 9 and 10. It can be as trivial as an effective amount of vitamin B12 or it can be a specific dosage of vitamin B12 administered intramuscularly, either 500 to 1,500 micrograms or about 1,000 micrograms.
Q. And would the addition of any of those dosages or routes of administration of vitamin B12 have been obvious to a person of ordinary skill in the art as of June 1999?
A. Yes.
Q. And what's the basis for that opinion?
A. For all the reasons we discussed earlier about the obviousness of adding vitamin B12 to the prior art.
Q. Okay. And can we look at the last limitation on your chart and your comparison between Claims 9 and 10 of the '209 patent and Claim 20 of the '974 patent?
A. Yes. The last limitation basically is the same. It's different words. One has A followed by B, and the other one has A before B.
Q. Okay. Did you also prepare a chart comparing Claims 12,

14, 15, and 18 of the '209 patent to Claim 20 of the '974 patent?
A. Yes.
Q. Okay. And with reference to your chart, can you explain again; can you walk through the first limitation and explain the comparison between Claims 12, 14, 15, and 18 of the '209 patent with Claim 20 of the '974 patent?
A. Well, the first and last limitation are exactly the same as what we previously discussed. The second limitation, again, it has the -- my error on the folic acid dose range. It's 350 to a thousand or 350 to 600 prior to the first administration versus the same dose range for the folic acid. And the -- and then there's the vitamin B12 limitations, which are now slightly different than in the previous claims and which -- and there's no vitamin B12 in Claim 20 of the '974 patent.
Q. And would any of those differences that you've identified -- I'm sorry. Are those differences that you've identified, would those differences have been obvious to a person of ordinary skill in the art as of June 1999?
A. Yes.
Q. And what's the basis for the obviousness?
A. The same as we've been discussing, the whole reason to add B12 to the prior art, the same reason these are obvious variance of Claim 20 of the '974 patent.

Q. Okay. Let's move on to talk about Claim 21 of the '209 patent. And have you prepared a chart that shows a comparison between Claim 21 of the '209 patent and Claim 20 of the '974 patent?
A. Yes.
Q. And can you explain with reference to this chart the comparison between Claim 21 of the '209 patent and Claim 20 of the '974 patent?
A. Well, the issues are exactly the same as for the previous claims. Again there's the error on this slide. The dose range of the folic acid in the '209 patent is 350 to 1,000 or 350 to 600. And the B12 here, it's the same B12 regimen we've been talking about but with the additional limitation of repeating the dose every six -- about every six to about every 12 weeks. Again, this is an obvious variant of Claim 20 of the '974 patent.
Q. And why is the additional limitation of wherein B12 is administered about every six to about every 12 weeks until pemetrexed treatment is discontinued, why is that an obvious variant?
A. And, again, it's for the same reasons I discussed previously. This would be routine medical practice.
Q. Okay. And now if we can move on to Claim 19 of the '209 patent. And have you prepared a comparison, a slide showing a comparison of Claim 19 of the '209 patent to Claim 20 of the

'974 patent?
A. Yes, I have.
Q. And can you explain the comparison that you've depicted on Slide 150 that compares those two claims?
A. Well, we've previously discussed the first, third, and fourth limitations in the context of the other claims. The difference on the second limitation is that Claim 19 of the '209 patent states to give the folic acid one to three weeks prior to the first administration of pemetrexed, and I also want to identify the error on the slide, on the dose range of the folic acid. It's 350 to 1,000 or 350 to 600.
Q. Okay. And would the schedule of administration of folic acid of one to three weeks prior to the first administration of pemetrexed have been an obvious variant of Claim 20 of the '974 patent?
A. Yes, it would.
Q. And why is that?
A. Again, this is routine medical practice. It accomplishes the goal of beginning to support and replete the -- with physiological doses of folic acid, one to three weeks prior to the chemotherapy to allow the folate stores to be repleted.
Q. Now, doesn't Claim 20 of the '974 patent specifically identify a different schedule of administration of folic acid of about one to 24 hours prior to administration of the antifolate?

A. It does say that in the claim, yes.
Q. Is there anything in the specification of the '974 patent about the schedule for administration of folic acid?
A. Yes, there is.
MR. PERLMAN: Objection.
THE COURT: What's your objection, Counsel?
MR. PERLMAN: The objection, Your Honor, is that for double patenting, if that is going to be the defense, it is based on the claims of the prior patent only, not the specification of the prior patent. If this relevant to the obviousness defense, then the patent as a whole is treated as any other reference in the prior art. But if this testimony is directed to double patenting, then it is based on the comparison of the claims of the earlier patent to the claims of the later patent.
MS. RAPALINO: And I respectfully disagree about the state of the law. Double patenting is a comparison of the claims of one patent to the claims of the other, but it's in view of the prior art. And in this unusual circumstance where the '974 patent is itself prior art to the '209 patent, having been published far more than a year prior to the filing of the application for the '209 patent, the entirety of the patent is available as prior art for what it would have taught to a person of ordinary skill in the art.
THE COURT: Well, I'll overrule and let her present

her evidence, and if you have some law that says I should disregard it, then we'll look at that later.

MR. PERLMAN: I'll do it in our later briefing. It's not worth a big thing right now, Your Honor.

THE COURT: All right. You may continue.

MS. RAPALINO: Thank you.

BY MS. RAPALINO:

Q. So if you turn in the specification of the '974 patent to Column 6, what does the '974 patent say about the schedule of administration of folic acid?

A. Well, Column 6 of the '974 patent basically makes it clear that the schedule of the folic acid is not critical. It states, "Although one single dose of the FBP binding agent, preferably an oral administration of folic acid, should be sufficient to load the folate binding protein, multiple dosing of the FBP binding agent can be employed for periods up to weeks before treatment with the active agent, to ensure that the folate binding protein is sufficiently bound in order to maximize the benefit derived from such pretreatment."

Q. And so what is the '974 patent specification teaching with respect to what would be an appropriate schedule of administration for folic acid prior to administration of pemetrexed?

A. The '974 patent teaches that you could give a single dose shortly before the chemotherapy and also says that you

could divide this dose over a period of weeks and start, just simply start with a low dose weeks earlier.
Q. Okay. And is there anything in the claims, even if we are limited to the claims, is there anything in the claims of the '974 patent that would include a schedule of administration of folic acid for weeks prior to administration of the antifolate or pemetrexed?
A. Well, yes. Because Claim 18 does not have a limitation regarding the exact interval between starting the folic acid and starting the antifol.
Q. And when you say antifol, is that a shorthand for antifolate?
A. Yes.
Q. Do you have an opinion as to whether a person of ordinary skill in the art would have had a reasonable expectation of success in practicing Claims 9, 10, 12, 14, 15, 18, 19, and 21 of the '209 patent in view of the '974 patent?
A. Yes.
Q. And what is that opinion?
A. It's my opinion that a person of ordinary skill in the art would have had a reasonable expectation of success of practicing the -- these claims.
Q. And when you say a reasonable expectation of success, what do you mean by that?
A. What I mean is that a person of ordinary skill in the art

would have expected to be able to achieve a therapeutic benefit with the combination of folic acid pretreatment, B12 pretreatment, followed by pemetrexed.

Q. Okay. So Dr. Ratain, I just want to summarize and make sure that your testimony is clear. In light of everything and all the prior art you've looked at, what did you conclude about the asserted claims of the '209 patent with respect to obviousness?

A. My opinion is that all of the asserted claims are obvious.

Q. And what's the basis for your opinion that all of the asserted claims are obvious?

A. My opinion is that the prior art taught a person of ordinary skill in the art how to modify the prior art to practice the asserted claims.

Q. And would the person of ordinary skill in the art have had a reasonable expectation of success that if they had added vitamin B12 at the claimed doses and schedules to a regimen of vitamin -- I'm sorry, of folic acid pretreatment with pemetrexed, would they have had a reasonable expectation of success?

A. Yes.

Q. And what is your opinion with respect to the asserted claims and obviousness-type double patenting over Claim 20 of the '974 patent?

A. My opinion is that all of the asserted claims of the

'209 patent are obvious variance of Claim 20 of the '974 patent.

Q. And again, what is the basis for your opinion that they are obvious variance of Claim 20 of the '974 patent?

A. When one rewrites these claims, it's very clear that there's only modest differences, and these modest differences are obvious variance, and the only significant difference is adding the B12. And a person of ordinary skill in the art would be motivated to add B12 for the same reasons as in my obviousness analysis.

MS. RAPALINO: Thank you, Dr. Ratain. I'm ready to pass the witness, although it looks like it might be the end of the day.

THE COURT: I think it's the end of the day. Do you want to start in the morning? We have to leave at 5:00 because they're going to do some work in the back of the courtroom at 5:00.

MR. PERLMAN: Your Honor, I think the parties have an issue they want to discuss with the Court anyway, so if your preference is that I not do 20 minutes, I'll just start fresh in the morning.

THE COURT: That will be fine.

MR. PERLMAN: That's fine with me.

THE COURT: We'll hopefully move a little faster tomorrow. Look at him. She got eight hours. You want eight

hours?

MR. PERLMAN: I don't want eight hours, but I do have a 151-page PowerPoint direct.

THE COURT: Hers was 151 also.

MR. PERLMAN: Hers was 151, so I do have more than a ten-minute cross is all I'm trying to express.

THE COURT: All right. Okay. All right. So witness, you may be excused for the evening, and we'll have you back at 9:00 a.m.

MR. WIESEN: Your Honor, as Mr. Perlman suggested, we have one dispute concerning a deposition designation that recently occurred. We've met and conferred about it. It's not pressing in that it needs to be decided today, but it is something that, given the possibility that Eli Lilly may want to play some of the designations, we thought we would flag the issue for you and see how you wanted to address it if that's okay.

THE COURT: Fine.

MR. WIESEN: My colleague, Mr. Cottler, will address it for us. I believe Mr. Genderson will address the issue for Eli Lilly.

THE COURT: Very good. This is Michael Cottler?

MR. COTTLER: Yes, Your Honor. And just one housekeeping thing. I believe Ms. Rapalino needs to move Dr. Ratain's exhibits into evidence before I proceed if that's

okay.

THE COURT: Come on up. Come on up.

MS. RAPALINO: Okay. Defendants offer the following trial exhibits into evidence: Trial Exhibit 1, Trial Exhibit 1507, 1508, 1151, 907, 401, 1087, 1443, 1036, 400, 916, 1087, 918, 384, 911. 911 as Mr. Perlman mentioned is two exhibits, the Hammond I abstract as well as the Niyikiza I abstract. Trial Exhibit 912, 910, 401, 502, 1443, which I think I mentioned before. 1336, 1204, 2059, 1374, and 1386. And to the extent that Mr. Perlman was willing to stipulate to the admission of Trial Exhibit 337, I was -- I would also propose that the parties stipulate to the admission of Trial Exhibit 76 and 330.

THE COURT: Come on up, Mr. Perlman. What is your response? First, do you have any objection to the first series?

MR. PERLMAN: If I was keeping up, I think that's right, Your Honor. I would like to reserve the right to check it overnight and if there's a problem, bring it up in the morning. That was pretty fast. I guess I do have an objection to admitting exhibits through a witness that the witness didn't talk about and were never put to him. I don't know off the top of my head what those exhibits are that they're asking me to stipulate to.

If there are more Eli Lilly-authored documents

submitted to the FDA, I can, I am happy to take a look when I get back to the office what they are, and if they stand in the same footing, I'll do the same stipulation. But I don't have perfect recall of the number of every exhibit in this case.

THE COURT: Is that fair, Ms. Rapalino?

MS. RAPALINO: That is fair, and I'll represent that those are. The reason I proposed that was because they are, like the trial exhibits, which we already, which we already have a stipulation. They are Lilly-authored documents to the FDA.

THE COURT: Okay. And he will look at those overnight?

MR. PERLMAN: Can I get just the numbers again?

MS. RAPALINO: Seventy-six, 330.

MR. PERLMAN: Seventy-six and 330? Okay.

THE COURT: 337 is the exhibit that's already been stipulated, correct?

MS. RAPALINO: Correct.

THE COURT: Okay.

MS. RAPALINO: And I'm sorry, I may have -- never mind. We've got them all.

THE COURT: Okay.

MS. RAPALINO: Thank you.

THE COURT: Okay. Thank you.

MR. COTTLER: Good afternoon, Your Honor.

THE COURT: All right, Mr. Cottler, I'm ready for you.

MR. COTTLER: Thank you, Your Honor. This is somewhat of an unusual scenario where we have a discovery dispute long after the close of fact discovery, in fact, on the first day of trial. And we are seeking Your Honor's guidance as to how to proceed with this issue.

As you may be aware, the parties had the pleasure of traveling to London to take the deposition of Dr. Hilary Calvert. Prior to that deposition, you may be aware there was a proceeding that took place in London. Lilly had opposed the Hague request, both in the U.S. and then following the letter of request, they opposed the English order issuing the deposition.

The deposition was granted over Lilly's objections at the end of July, and, in fact, I believe it was the day before the pretrial conference. Pursuant to Lilly's insistence, defendants had to disclose, give notice of documents that they intended to use with Dr. Calvert prior to the deposition. Also, Lilly had insisted that the deposition took place, the topics should be narrowed. The English court did narrow the topics as Lilly insisted.

Prior to the deposition, defendants complied with the order that the defendants gave Dr. Calvert notice of documents they intended to use at his deposition. There were

a couple of exceptions. Those were documents that Dr. Calvert produced the day before the deposition, so obviously those couldn't have been given notice of four days before the deposition.

During the deposition, it became evident that Dr. Calvert had prepared for his deposition with counsel for Lilly the day before deposition, and during that preparation, they discussed the topics that would come up at the deposition, and they also looked at documents, some of which hadn't been disclosed to defendants prior to the deposition. And then, at the actual deposition, the counsel for defendants questioned Dr. Calvert for approximately two and a half hours. After that, counsel for Lilly questioned Calvert for about the same amount of time, and here's where the issue comes up.

We believe that during counsel for Lilly's questioning, examination of Dr. Calvert, there were a number of questions that came up that sought testimony that was outside the scope of the topics that had been narrowed by the English court. In fact, a number of those -- a number of the questions fell within the category of topics that was actually once in the letter of request but was subsequently removed.

Additionally, there were a number of questions about documents that were introduced at the deposition but hadn't been disclosed to defendants prior to the deposition, so there was no notice of those documents. There were a number of -- I

guess there were a handful of prior references that were shown to Dr. Calvert at the deposition, and there was no prior notice of those documents. So, Your Honor, we're seeking to preclude Lilly -- let me back up a second.

The parties have exchanged designations of Dr. Calvert's deposition pursuant to an agreement. The parties have also exchanged objections and counter designations. We know now that Lilly plans to play some of Dr. Calvert's testimony on Friday, if they have time. And so, we are seeking to preclude Lilly from relying upon any of the testimony that falls within the scope of -- I'm sorry -- that falls within the scope of topics that was excluded from the letter of request in addition to any testimony that was based on exhibits that wasn't disclosed to defendants prior to the deposition.

This doesn't need to be resolved right here, right now. We're here seeking your guidance as to how to proceed. We are prepared to file a brief tonight if Your Honor would like to have this resolved prior to the time that Lilly seeks to play Dr. Calvert's testimony.

THE COURT: Okay.

MR. GENDERSON: Your Honor, may I be heard briefly?

THE COURT: You may.

MR. GENDERSON: Your Honor, Mr. Cottler and I were the lucky ones who --

THE COURT: You're Grossman, correct?

MR. GENDERSON: Genderson -- I'm sorry, Bruce Genderson.

THE COURT: Genderson, okay. Get my seating chart, okay.

MR. GENDERSON: And I think this could be resolved right now. I don't see this as a complex issue. The UK court issued an order that did not require us to do anything. They effectively adjudicated both of the issues that are being raised here because there was an examiner that the court appointed to be at the deposition. They raised these issues, they were sustained on some questions and overruled on others. But this is a UK issue that was ruled on by the UK court.

The order that Mr. Cottler referred to, Your Honor, was an order that required that the defendants give the witness, not us, but the witness notice. Because under UK procedure, the witness is entitled to know ahead of time the documents that are being asked.

That order didn't require them to give notice to us, and it didn't say anything about us. We, Mr. -- Dr. Calvert agreed to meet with us for a few hours before the deposition -- the day before the deposition. I showed him -- I actually brought three boxes of documents that I had no idea. This was all done at the last minute while we were preparing for trial. I showed him some documents. The one --

some of them he had no recollection of, I didn't use those; others he did and said he was familiar with them. Those are the only ones I asked. I gave him -- I don't think I had any obligation to under the order, but I gave him notice.

Mr. Cottler made the same objection. The examiner who was appointed by the Court there overruled it and said they could proceed. He asked Mr. Calvert if he was familiar with the documents, he said "yes." He then said you could take up any other issue with the U.S. court as to that.

And then, as to whether something was in the scope of the order itself in terms of the questions, Mr. Cottler objected to a number of those questions. The examiner sustained at least one, I think more of those objections, and I -- and then I was precluded from asking.

On many others I explained why it was relevant. The examiner ruled. This is a UK issue to protect the witness. It has nothing to do with whether these documents are admissible or relevant here; and indeed, Your Honor, we have a stipulation between the parties that was entered into when we were discussing this whole issue that said no later than two days after Dr. Calvert's deposition, any party must give notice if they intend to use portions of the deposition for any purpose relevant to the case. It was clear that if the testimony was relevant, it was admissible. This testimony is relevant. You heard Mr. --

THE COURT: Did you give notice?

MR. GENDERSON: Yes, we did, Your Honor. We did do that right after the deposition. Mr. Perlman explained why this dep -- this is admissible. This is a witness who was an expert, who was listening to the same information that we heard about today, and the evidence will show he and other experts on this advisory panel kept saying "this is too dangerous. Don't do it."

The reason they want to preclude this evidence is not because we tricked them or we used evidence. I've never had a deposition where I had to give notice to the other side, and the order didn't require that, only to the witness. They don't like this evidence because it's very probative of the case, and I think the Court should hear it.

The Court could make judgments about how relevant it is, whether Dr. Calvert was properly appraised of the evidence. Dr. Calvert was -- I did not ask him about a single document that he wasn't familiar with, Your Honor.

THE COURT: Okay. Thank you.

MR. COTTLER: May I respond?

THE COURT: You may.

MR. COTTLER: Unfortunately, Your Honor, the events that relate to this Hague proceeding were over the course of several months, and I think it would be best, Your Honor, if these issues were addressed in a brief to set forth the whole

event, the whole line of events that led to where we are today. But just to respond to some of Mr. Genderson's points, this is about fundamental fairness.

We had -- defendants had asked for a Hague request seeking certain testimony from Dr. Calvert. Lilly then went ahead and opposed it and sought restriction on the topics the defendants had asked for. That -- the Hague proceeding wasn't -- it was very time-consuming and burdensome on defendants, and for Lilly to be able to ask questions now that are outside the scope of the narrow topics is just unfair to defendants. And we submit that fundamental fairness would dictate that Lilly should be precluded from relying upon any testimony that was elicited from outside the scope of the deposition topics.

The idea to provide disclosure of documents to Dr. Calvert prior to his deposition, in fact, came from Lilly. In the English Hague proceedings, they have these arguments called "skeleton arguments," and this would be something that Your Honor would see in a brief that we would submit, but essentially, a skeleton argument is a brief that's submitted to an English court prior to a hearing.

And the skeleton argument, Lilly had told the court that in the event that the deposition is granted, Calvert should be given advanced notice of any documents. Lilly didn't specify defendants must give notice, they just said

Dr. Calvert must be given notice, and what was agreed upon was that Calvert would be given notice of documents four days before the deposition. It doesn't sound like Dr. Calvert was given notice of any documents from Lilly four days before the deposition; if any, it was a day before the deposition.

But regardless, back to fundamental fairness, just because only defendants were required to give notice to Dr. Calvert doesn't mean that Lilly shouldn't have given notice to defendants of the documents, so the defendants would be prepared to take Dr. Calvert's deposition and be prepared to respond to any testimony that Lilly would elicit from Dr. Calvert.

And one more point, Your Honor. Mr. Genderson had mentioned a stipulation that the parties had entered into, and that stipulation dictated that parties could use any relevant testimony. That stipulation was entered into, brought before we knew that the topics would be narrowed by the English court. So, I mean, to the -- the defendants couldn't have anticipated the way in which Dr. Calvert's topics would have been narrowed at the time they entered the stipulation.

So to say that the stipulation granted Lilly the right to ask questions that are outside the scope of the narrow topics is just incorrect. But again, Your Honor, we submit that the facts in this case are best addressed in a brief that could be filed today.

THE COURT: You can have a brief today?

MR. COTTLER: Yes, Your Honor.

THE COURT: Come on back, Mr. Genderson.

MR. PERLMAN: Your Honor, they've known about this issue. They wait and they obviously --

THE COURT: Prepared a brief already.

MR. GENDERSON: Now we're in the middle of a trial. This is not a complicated issue, Your Honor, and it's already been ruled on by the examiner. They raised these issues. These are UK procedure issues, and they were overruled, and now they shouldn't have a second bite at this apple. And the documents I used frankly, Your Honor, were -- 90 percent of them were meeting minutes of meetings that were the topics of the request.

The notion that they didn't have any idea what documents I was going to use, the subject of the request for meetings were the antifolate advisory board, and you will see when we play the deposition, Your Honor. What I used were minutes of those meetings. How could they not have thought that that was going to be what we were going to do?

I didn't bamboozle them with any surprise documents, but there was no requirement. The order said, give them to Dr. Calvert. Dr. Calvert didn't object. This is Dr. Calvert's objection, not their. And there's no fundamental unfairness. This is a deposition.

THE COURT: Okay. All right. Mr. Cottler, you have a brief already?

MR. COTTLER: We can file it tonight, Your Honor.

MR. GENDERSON: We didn't know this was coming.

THE COURT: I know. I'll give you time to file a brief, also. I'll read the briefs, because you're not intending on calling the witness until Friday?

MR. GENDERSON: Friday. Yes, Your Honor, but I'm not sure since we're in court.

THE COURT: You have a big team. One of those 20 lawyers over here can get something together. How much time do you need? He's going to file his tonight and you can respond.

MR. PERLMAN: Okay. If we intend to play this video on Friday, if we got you something by the end of Wednesday, would that give you sufficient time to rule?

THE COURT: Yes.

MR. PERLMAN: Can I ask -- it sounds like the brief is ready. Can I ask that it be filed earlier than 11:59 p.m. so that we have some opportunity to work on it this evening?

THE COURT: What time are you going to file it? Probably when they walk out of this room.

MR. PERLMAN: Can they hand me a copy right now and we can get started?

THE COURT: Do you have it?

MR. WIESEN: We have to coordinate the exhibits that go with it, but we'll coordinate it and we'll get it done as quickly as we can. If we can get them a brief without the exhibit, we will do that.

THE COURT: They can probably hand you a brief without the exhibits right now.

MR. PERLMAN: That would be great. That would be great, Your Honor.

THE COURT: Get something docketed before 9:00 p.m.

MR. WIESEN: We should be able to do that, Your Honor.

MR. PERLMAN: If we can get started on the brief, we can get started. You know, probably would have been more efficient to start the talking before they wrote the whole brief. That's neither here nor there, Your Honor.

MR. COTTLER: Just for -- okay, I'll go ahead. Sorry. Just for clarification, we just received Lilly's designations this week and exchanged objections on Saturday, and we met and conferred this morning, so this is ripe right now. We couldn't have resolved this any sooner.

THE COURT: All right. Well, get your brief docketed by 9:00 p.m., and you can go ahead and give Lilly's attorneys a copy of the brief without the exhibits. And Lilly, you will have something to me by the end of -- sometime Wednesday night?

MR. PERLMAN: We'll get it to you Wednesday.

THE COURT: And we'll have a ruling for you by Friday morning.

MR. PERLMAN: That would be excellent, Your Honor, and we will go -- just to put it on the table, we'll go ahead and get the video ready to go on the assumption that we can do the full approach, and if you cut it back or you do something, we can always edit. But what I don't want to do is wait until Friday morning to start that process, because I don't want the Court to be waiting for anything.

THE COURT: That's fine, okay.

MR. COTTLER: Thank you.

THE COURT: Anything else before we adjourn?

MR. WIESEN: Nothing else, Your Honor.

THE COURT: Anything else?

MR. PERLMAN: No.

THE COURT: Okay. We'll see everyone at 9:00 a.m., bright and early.

THE COURTROOM DEPUTY: All rise.

(Proceedings adjourned at 4:59 p.m.)

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CERTIFICATE OF COURT REPORTER

I, David W. Moxley, hereby certify that the foregoing is a true and correct transcript from reported proceedings in the above-entitled matter.

/S/ David W. Moxley September 27, 2013

DAVID W. MOXLEY, RMR/CRR/CMRS
Official Court Reporter
Southern District of Indiana
Indianapolis Division